VOLUME 101 • MAY 1958 • NUMBER 5

A.M.A. ARCHIVES OF

INTERNAL MEDICINE

On Teaching the Care of the Patient
Charles S. Davidson

Digitalis Antagonism
Alexander C. Keyl

Gastric Ulcer
Richard F. Jones, Randolph Clements, and Clarence C. Pearson

Urinary 17-Hydroxycorticoid and Uropepsin Levels with Psychological Data
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The Gastric and Jejunal Mucosae in Healthy Patients with Partial Gastrectomy
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Syphilis
Herman Beerman, Ira L. Schamberg, Leslie Nicholas, and Marvin S. Greenberg

Progress in the Long-Term Management of Coronary Artery Disease
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TABLE OF CONTENTS

VOLUME 101 MAY 1958 NUMBER 5

EDITORIALS

PAGE

On Teaching the Care of the Patient
Charles S. Davidson, M.D., Boston 847

ORIGINAL ARTICLES

Digitalis Antagonism
Alexander C. Keyl, Ph.D., Chicago 849

Gastric Ulcer
Richard F. Jones, M.D.; Randolph Clements, M.D., and Clarence C. Pearson, M.D., Seattle 855

Urinary 17-Hydroxycorticoid and Uropepsin Levels with Psychological Data
Henry M. Fox, M.D.; Benjamin J. Murawski, Ph.D.; George W. Thorn, M.D., and Seymour J. Gray, M.D., Ph.D., Boston 859

The Concept of Early Diagnosis in Strokes
Robert G. Siekert, M.D., and Clark H. Millikan, M.D., Rochester, Minn. 872

A Twenty-Year Appraisal of BCG Vaccination in the Control of Tuberculosis
Joseph D. Aronson, M.D.; Charlotte F. Aronson, A.B., and Helen C. Taylor, R.N., Philadelphia 881

Hereditary Spherocytosis
Capt. William F. Denny (MC), U. S. A. F.; Robert M. Bird, M.D., and Merlin K. DuVal, M.D., Oklahoma City 894

Acute Glutethimide (Doriden) Poisoning
George E. Schreiner, M.D.; Leonard B. Berman, M.D.; Renato Kovach, M.D., and H. Allan Bloomer, M.D., Washington, D. C. 899

The Relationship of Abnormal Vascular Responses to Retinopathy and Nephropathy in Diabetics
Jørn Ditzel, M.D.; Lynn Sargeant, M.D., and William B. Hadley, M.D., Boston 912

Chronic Uremia Due to Polycystic Renal Disease Treated with the Artificial Kidney
S. Nakamoto, M.D., and W. J. Kolff, M.D., Cleveland 921

Radioactive Cyanocobalamin (Vitamin B_{12}) in Renal Disease
Arthur L. Dunn, Ph.D.; John R. Walsh, M.D., and Joseph M. Holthaus, M.D., Omaha 927

X-Ray Manifestation of Peptic Ulceration During Corticosteroid Therapy of Rheumatoid Arthritis
Theodore F. Hilbish, M.D., and Roger L. Black, M.D., Bethesda, Md. 932

The Gastric and Jejunal Mucosae in Healthy Patients with Partial Gastrectomy
Fred Lees, M.B. (Sheffield), M.R.C.P., Sheffield, England, and L. C. Grandjean, M.D., Copenhagen 943

REVIEWS OF INTERNAL MEDICINE

Syphilis (CONCLUDED)
Herman Beerman, M.D.; Ira L. Schamberg, M.D.; Leslie Nicholas, M.D., and Marvin S. Greenberg, M.D., Philadelphia, with the Collaboration of T. Guthe, M.D., and C. J. Hackett, M.D., Geneva, Switzerland 952

Progress in the Long-Term Management of Coronary Artery Disease
Mohinder P. Sambhi, M.B., B.S., and Henry A. Zimmerman, M.D., Cleveland 974

EVOLUTION OF MODERN MEDICINE

T. J. Maclagan and the Treatment of Rheumatic Fever with Salicin
Mary Woodruff Snead, B.A., and Jerry K. Aikawa, M.D., Denver 997

CONTRIBUTIONS OF BASIC SCIENCE TO MODERN MEDICINE

The Significance of Nonesterified Fatty Acids in Plasma
Vincent P. Dole, M.D., New York 1005

BOOKS

Reviews by Dr. William B. Bean and Others 1009

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VOLUME 101 MAY 1958 NUMBER 5

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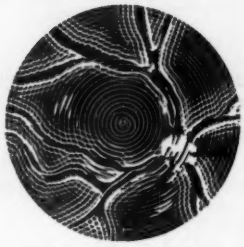

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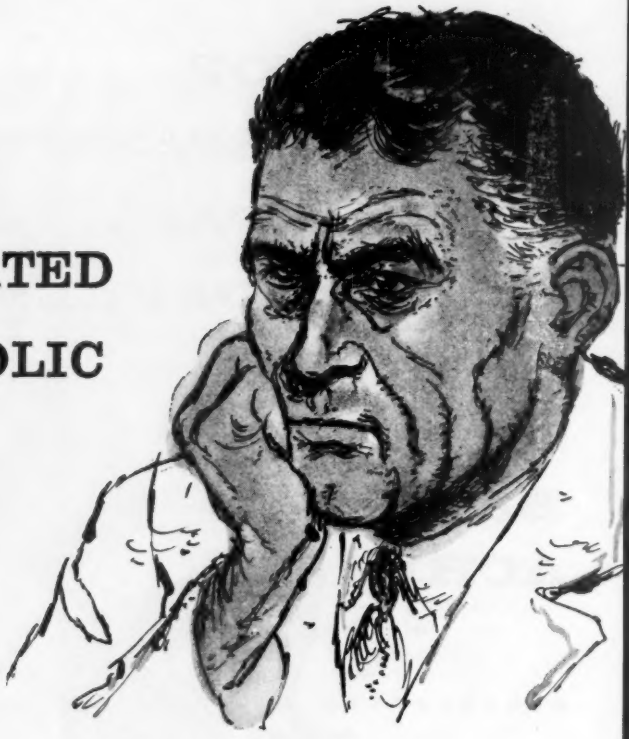

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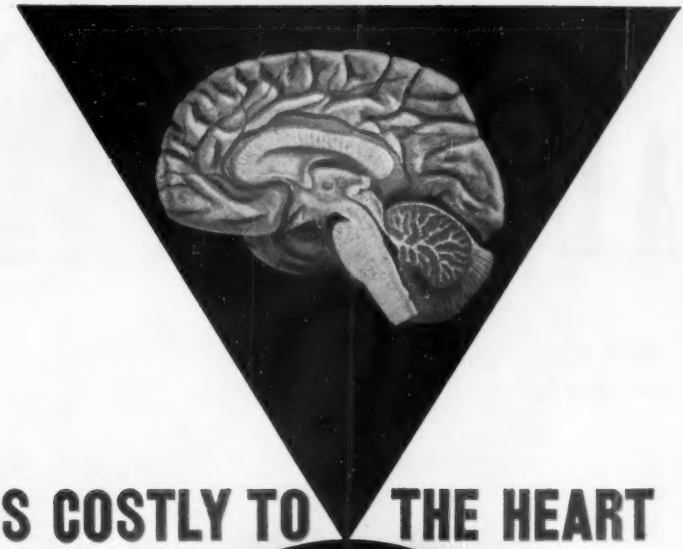

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Editorials

On Teaching the Care of the Patient

To the medical studies of thirty years ago Francis Weld Peabody wrote, "The secret of the care of the patient is caring for the patient" (Peabody, F. W.: The Care of the Patient, J. A. M. A. 88:877, 1927). When this was written, the acceleration of discoveries in scientific medicine was just beginning. Insulin had only recently been found; liver extract for pernicious anemia was soon to be available. Fluid and electrolyte balance were little known by practitioners and medical students. Potent, sometimes dangerous, medicines, like hormones and antibiotics, were years away, and the hospital clinical chemistry laboratory could not tell the doctor the values for transaminase, ceruloplasmin, or hydroxycorticoids.

Today, in a somewhat different context, the Peabody aphorism is as apt as it was in 1927, or more so. On many sides one hears complaints that medical students are taught only scientific medicine or that the patient is lost sight of by students and teachers because the welter of laboratory results and consultative studies interfere. Is it possible for medical students to learn the frightening mass of scientific details and also to learn to care for the patient? This is a real feat today, no matter who teaches them. I believe it not only is possible but must be done, as future practitioners must care for patients with every possible scientific aid. How to proceed? Given intelligent and interested students, much hangs on the teacher.

Who are the teachers, and what qualifications do they now have? Many are "full time" pursuing active research programs or accomplishing little teaching or research because of heavy administrative burdens (the latter often secretly enjoyed, be it admitted). They are fit best to teach matters akin to their own research or subspecialty, sometimes little else. Part-time practice and teaching is a commendable combination, but such a busy career often precludes keeping up with or, better, ahead of the students' knowledge of scientific medicine. As a consequence, the students, and often interns and residents, are left to themselves in the task of putting together science and art in the patient's care. Do our teachers spend sufficient time and effort to be sure that students and interns know how to "take a history" or how to look into the background and mores affecting the patient and his disease? Many psychiatrists feel that this is their province and prerogative. If so, who then studies the physical examination and laboratory findings and attempts from his wide experience and knowledge to put all these data together? Surely not the psychiatrist. Yet, unless the internist is prepared to accept this responsibility as a teacher, it will be divided among psychiatrists, clinical pathologists, and others, and medical care will suffer a mortal blow. Is today's internist—part time or full time—always as capable as he should be?

Perhaps the day has returned for the internist as a full-time occupation again to study and teach the care of the patient in its expanded form, with few ad-

Submitted for publication Jan. 20, 1958.

From the Thorndike Memorial Laboratory and the Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

ministrative duties and with research only as a hobby. The "history," physical examination, laboratory and consultant's studies, and, even more, the intellectual process of integrating these data of varied validity and source into a comprehensible whole—this should be the duty and scholarly pleasure of the physician-internist as a full-time teacher.

If this concept of the full-time teacher is to be brought alive for more of our medical schools, several hurdles must be jumped. First, teaching medicine must become recognized as a first-class academic pursuit for a full-time physician. Second, administrative duties must not be burdensome. Third, research must not be expected, in fact, should not be allowed, to replace the major efforts of scholarship and teaching, except as a hobby. Such a change in philosophy for our medical schools is made difficult by the large sums of money thrown into research. There is pathetically little for teaching as such. Academic promotion (and salary) for these full-time teachers would be based not on published experimental work but rather on their scholarly knowledge and ability to stimulate young minds in the difficult, almost insurmountable, task of bringing scientific knowledge and human understanding together to bear in a logical fashion upon the patient's care.

Researchers would of course remain, for it has become axiomatic that research adds life and stimulation to medical education. Specialists, experts in many fields, and part-time teachers would continue to be necessary, but at least a few others would be encouraged to dedicate their lives to teaching the care of the patient by precept and by example.

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Digitalis Antagonism

Part I

ALEXANDER C. KEYL, Ph.D., Chicago

The research of A. Szent-Györgyi and co-workers [1] on the biochemistry of muscular contraction, while not universally accepted with respect to certain details of energy transfer, has provided a useful mechanochemical model of the events occurring in the contraction of the myocardium. The purpose of this paper is an attempt to apply some of the mechanical aspects of this hypothesis in a definitive manner to acute digitalis intoxication and to avoid for purposes of simplification the controversial issues involved in consideration of the effect of digitalis on the important energy-yielding and energy-utilizing biochemical mechanisms.

At the cellular level, Hajdu and Szent-Györgyi [2] assign a regulatory function to digitalis with respect to the creation of the proper ionic environment for optimal contraction of the actomyosin protein complex in heart muscle. The experimental basis for this concept is the study of the isometric tension developed by the isolated frog ventricle under a variety of experimental ionic conditions. An interesting conclusion drawn from this work presents a challenge to modern bioassay evaluations of the therapeutic potencies of digitalis preparations and questions the classical concept that digitalis toxicity is a prerequisite for clinical effectiveness. Because digitalis is assayed on its ability to produce fatal contracture, Szent-Györgyi argues that an "ideal" digitalis capable of correcting the pathological ionic imbalance without causing contracture would be adjudged impotent by bioassay. (It is beyond the scope of this paper to explore this point, but it should be mentioned that possibly both toxic and therapeutic properties may reside in the same chemical moiety, and if these properties exist in some fixed ratio, the measurement of either property would constitute an indirect measurement of the other. The point, however, is well made in regard to the use of bioassay as a screening procedure for nontoxic digitaloids.) By use of the frog-ventricle preparation, certain steroids and specific animal sera were shown to mimic the therapeutic actions of digitalis in ion regulation without the superimposition of the contracture-producing toxic effects. Recently, Titus and Hajdu [3] have actually isolated a cardioactive principle from bovine adrenal medulla, heart, plasma, and liver which is capable of ion regulation without apparent toxicity. The material was characterized chemically as a monopalmitoyl glyceryl phosphoryl choline, and its structure was established by chemical synthesis. This β-lysolecithin on rearrangement to its α-isomer loses its essentially therapeutic properties and develops toxic actions similar to those of the digitalis saponins.

Submitted for publication Oct. 8, 1957.

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The physiological system used by these workers to investigate the parameters affecting myocardial contraction was the Bowditch "staircase" phenomenon [4] in the isolated frog heart. In this preparation, the isometric tension developed by the electrically stimulated ventricle is proportional to the frequency of stimulation and is an artifact which results from the elevation of the cold-blooded heart to room temperature, which may readily be abolished by lowering the heart temperature to 5 C or by removal of potassium ions from the perfusion medium. By this procedure, Hajdu [5] was able to study ion shifts from the electrically stimulated ventricle into the perfusion fluid and establish the ionic equilibrium necessary for normal contraction as evidenced by disappearance of the "staircase." He found that under "normal" conditions of contraction, a fixed amount of potassium left the heart cells, which reentered before the next contraction at a rate depending on the condition of the cell membrane. Blocking reentry of potassium by means of digitalis under "staircase" conditions abolished the "staircase" and permitted resumption of normal activity. If the digitalis blockade was carried to the point of decreasing internal cellular potassium to a critical level, contracture resulted. From these studies, digitalis emerges as a regulator of potassium reentry into heart cells by affecting membrane permeability to create proper conditions for efficient contraction. Extension of this concept to embrace the condition of digitalis intoxication implies that if the digitalis-induced potassium reentry blockade is too effective, a negative potassium balance is created in the cell and deterioration follows. The foregoing account of the digitalis-potassium relationship provides a quasitheoretical basis for the use of potassium in digitalis poisoning.

From the time of Ringer [6] to the present, a voluminous literature has accumulated on the effect of circulating electrolytes and their effect on myocardial contraction. Various intact experimental animals and isolated heart preparations have been used to study the synergism and antagonism of various ions with respect to digitalis action on the heart to give support to the idea that potassium is a digitalis antagonist. In fact, the use of potassium chloride by Buff [7] on a purely empirical basis to combat undesirable side-effects of digoxin preceeded the current well-documented evidence of this antagonism. Perhaps the most elegant experimental evidence of the interplay between body potassium levels and digitalis activity is embodied in the hemodialysis experiments of Lown and co-workers.[8] These authors were able to demonstrate a myocardial threshold to the toxic effects of acetyl strophanthidin which was related to body potassium balance by means of the artificial kidney in both animal and human subjects. The requirements for digitalis toxicity could be varied from as much as 240% of normal when body potassium was increased during the titration dialysis to as low as 60% of normal by potassium removal. In their monograph "Current Concepts in Digitalis Therapy," [9] Lown and Levine suggest that the most important cause of the rise in the incidence of digitalis toxicity may be the electrolyte manipulation associated with general therapy of the decompensated patient. There can be little questioning of the rationale of potassium replacement therapy in those cases of digitalis intoxication induced by potassium depletion irrespective of the cause of the potassium deficiency. In spite of the reported success of potassium chloride alone or in conjunction with procainamide as a digitalis antagonist, there are also reports that this type of antagonism may be prophylactic in nature rather than antidotal.[10]

In this laboratory, the problem of digitalis toxicity has been under investigation from the toxicological standpoint of acute poisoning uncomplicated by electrolyte depletion or variation. Under these circumstances, a modification of some of the above concepts may be in order. The point of departure was the finding [11] that the acutely K-stro-

phanthin-poisoned dog was more sensitive to the lethal effect of intravenously administered potassium chloride than the normal dog.

Experimental Procedure

Female dogs of approximately 10 kg. in weight were anesthetized with pentobarbital (Nembutal) (30 mg. per kilogram) administered intraperitoneally; both left and right femoral veins were exposed for blood samples and injections; the urinary bladder was catheterized at the level of the trigone for urine samples; ECG electrodes were applied to the four limbs, and a control tracing was taken. K-strophanthin N. F. (0.16 mg. per milliliter), was then administered intravenously at the rate of 1 ml. every 5 minutes until the desired level of toxicity was reached, as denoted by the ECG tracing (usually bidirectional ventricular tachycardia). Aqueous potassium chloride (1%) was then infused at a constant rate (2.6 mg. per kilogram per minute, average). Blood and urine samples were taken at appropriate intervals for potassium analysis, and the cardiac effects of the potassium chloride infusion were followed by electrocardiographic tracings. In the control group of dogs, the procedure was identical, with the exception of the K-strophanthin administration. Potassium analyses were made using the Beckman DU Spectrophotometer with flame attachment. The mean lethal dose for the two groups was calculated from the body potassium load at death, which represents total administered potassium chloride less the amount lost in the urine. The mean lethal dose of the control group of seven dogs was 367 mg. per kilogram ±145, while that of the K-strophanthin-intoxicated group of 10 dogs was 117 mg. ±39. The difference between these mean values is significant at the 1% probability level. The terminal plasma potassium levels for the two groups were approximately the same; 14.4 mEq. per liter for the normal dogs and 14.1 mEq. per liter for the poisoned dogs.

An unexpected finding in the strophanthin-poisoned dog series, however, was that in no case was an abnormal ECG reversed toward the normal in spite of the fact that plasma potassium had been increased to fatal levels in each case. An explanation of this fact may lie in the possibility that in the acutely poisoned dog heart, potassium reentry is completely blocked by the K-strophanthin in spite of the artificially elevated plasma potassium gradient favoring reentry. The ability of digitaloids to block active transport of both sodium ions and potassium ions has been shown by Schatzmann [12] and Kahn and Acheson [13] in mammalian erythrocytes. The reentry of potassium released by contraction of the heart before the next contraction is an example of conventional active transport because the reentry occurs against a concentration gradient. The degree of blockade of active transport was shown to be proportional to the dose of digitalis. Schatzmann concluded that this type of interference with active transport was unlike that which occurs with monoiodoacetate. It is possible that this graded toxic response to dose may explain and help resolve some of the conflicting reports concerning the effectiveness of potassium chloride as a digitalis antagonist. If the digitalis toxicity is mild in terms of the degree of interference with active potassium transport, a rise in plasma K may aid the faltering potassium pump. If the degree of toxicity is sufficiently great to completely block the potassium pump, raising extracellular potassium in form of chloride merely aggravates the situation by superimposing the additional hazard of potassium toxicity.

On the supposition that the relatively high degree of ionization of potassium chloride at blood pH might be limiting factor with respect to penetration of the heart cell membrane, a search was instituted for organic potassium salts of low dissociation characteristics at the physiological pH.[14] (Davson and Danielli [15] have shown that for any given substance the neutral molecule penetrates cell membranes better than the corresponding ion.) The acid dissociation curves for the salts studied up to the present time are shown in Figure 1, in which per cent ionization is plotted against pH. Each of the salts of this series was then substituted for the potassium chloride used originally in the attempted antagonism of acute K-strophanthin toxicity. The rate of potassium infusion was regulated to correspond to that used in the potassium chloride experiments in terms of total potassium infused per unit time, and Figure 2 shows the incremental rise in plasma potassium plotted against the loading of each salt

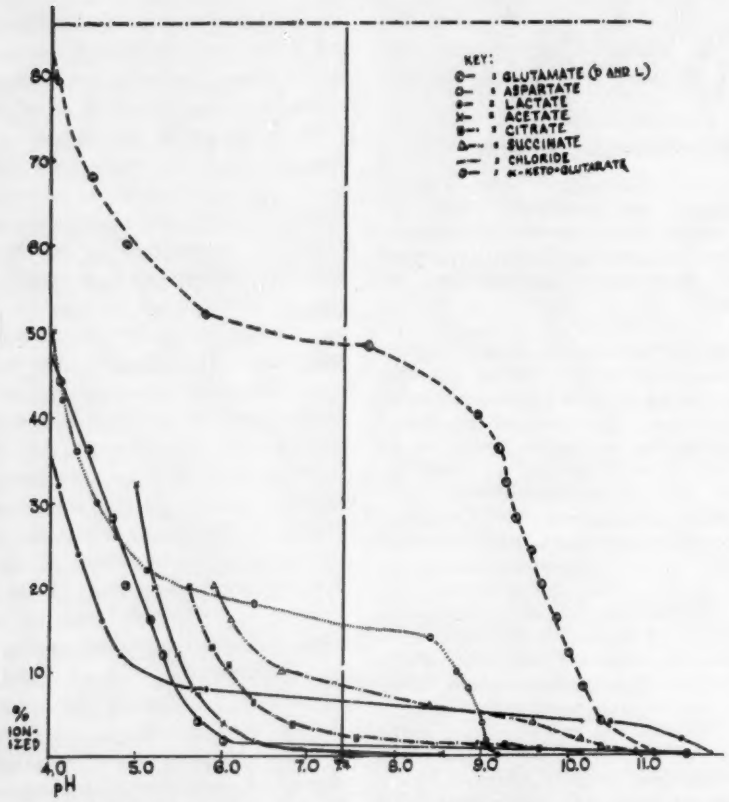

Fig. 1.—Acid-dissociation curve of various potassium salts. Ionization of potassium salts of weak acids at varied pH.

expressed as cubic centimeters of 1% KCl. In this way the effect of the anion differences on the molecular weight of the salt is eliminated and a direct comparison of the individual salt with potassium chloride made possible. The criterion used in evaluating penetration of strophanthin blockade was reversal of the abnormal ECG to the normal. Because this study is still in progress, only the qualitative results will be reported in this paper for purposes of completing the development of a mechanical description of digitalis toxicity.

Of all the salts studied, potassium in the form of α-ketoglutarate and L-glutamate were the only ones capable of reversing the strophanthin-induced abnormal ECG. Of the two the L-glutamate seems preferable because of its relatively low order of intrinsic potassium toxicity. The α-ketoglutarate salt is quite toxic and nearly approaches the toxicity of potassium chloride in the poisoned dog. It has been impossible to correlate either toxicity or ability to reverse the abnormal ECG with the degree of ionization of the salts at blood pH. In terms of the distribution of the L-glutamate in blood, the incremental rise in plasma potassium in the poisoned dog approximates that of potassium chloride in the normal dog. For purposes of comparison, the load line for plasma potassium administered as chloride in the normal dogs is shown in Figure 2, labeled as "normal infused."

It is premature to speculate about the mechanism of the α-ketoglutarate and L-glutamate reversal of K-strophanthin toxicity under circumstances where the chloride is

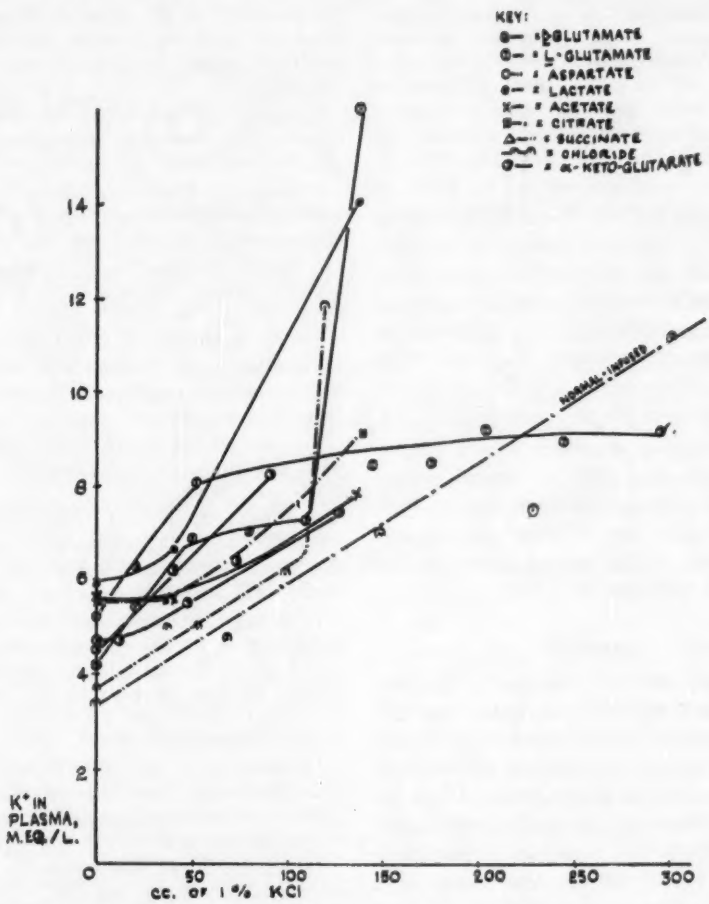

Fig. 2.—Rise of plasma K^+ with loading of salts. Potassium-loading curves for various potassium salts. Rates recalculated to be equivalent to cubic centimeters of 1% KCl per unit of time.

ineffective. It is conceivable that this action of these two salts is related to mechanism described by Krebs, Eggleston, et al.[16,17] in their experiments with potassium uptake in potassium-depleted ox retina cells. They found that the glutamate ion was necessary to reestablish in vivo sodium and potassium values in the depleted cells immersed in a nutrient medium. In this connection, the glutamate ion promotes active transport of potassium. Alpha-ketoglutarate promotes active transport of potassium in kidney cells in a similar fashion.[18]

In conclusion, the fortuitous, albeit inadvertent, application of L-glutamate in a clinical situation permits the presentation of a case history as a matter of interest.

A 65-year-old woman was rehospitalized on complaint of recurrence of arthritic pain. During observation, chest x-rays showed congestive heart failure with evidence of pulmonary edema, and a regimen of digoxin therapy was begun. After 12 days, signs of severe digitalis intoxication developed with complete heart block. At the same time, renal shut-down occurred and blood ammonia was found to be 250μg. per 100 cc. Potassium glutamate infusions were instituted for management of the hepatic coma, and this resulted in rapid reversal of the abnormal ECG. It was most significant that urinary potassium excretion was low (40 mEq. in three days while 15 gm. of potassium glutamate was being administered) and

that serum potassium did not rise above normal during this period. A prior infusion of potassium chloride (24 hours) caused a rise in serum potassium to 6.6 mEq. per liter. Initiation of glutamate infusion caused the serum potassium to drop to 5.1 mEq. per liter, although potassium was still being administered at the same rate.

This case is of interest not so much as an example of digitalis intoxication yielding to potassium glutamate therapy but as demonstration of the difference in distribution of potassium in the blood when administered as chloride and when given as glutamate in a case of severe poisoning. Figure 2 shows a similar difference in distribution of the same two salts in the poisoned dog.

The quantitive treatment of the animal, experimental data, and the clinical evaluation of the glutamate management of digitalis intoxication currently in progress will be published in the second paper of this series as a collaborative effort.

Summary

An attempt has been made to differentiate between mild digitalis intoxication and severe intoxication on the basis of how these extremes respond to antagonism by the potassium ion. It has been postulated that the primary defect may involve digitalis interference with active transport of potassium to the heart cells, and this interference is in proportion to the dose of digitalis. In mild cases, it appears that potassium in any form may be effective in overcoming the ionic deficit, whereas in severe cases, the anion of the potassium salt may be a factor in determining its effectiveness.

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Gastric Ulcer

An Analysis of One Hundred Sixty-One Cases

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The treatment of gastric ulcer is controversial largely because of the possibility that an early gastric malignancy may be overlooked. Proponents of surgical treatment for all patients with gastric ulcer offer the following facts in support of their thesis. First, the issue of whether the lesion in question is benign or malignant is rapidly settled. Some series show that the cure rate after gastric resection of a malignant lesion posing as a benign ulcer is much higher than that of the usual case of gastric carcinoma.[1] Second, the surgical mortality rate is very low, being in the range of 2%.[2] Third, the result of gastric resection is good in that the recurrence rate is small and the incidence of serious complications, such as dumping or diarrhea, is low.[3] Finally, there are several reports of high recurrence rates in patients treated medically.[2,4]

Other series report that medical treatment in carefully selected cases has been successful in that patients' ulcers heal, stay healed, and do not subsequently develop into carcinoma of the stomach.[3] Therefore, it appears that certain selected cases deserve a medical trial of therapy, providing they can be closely followed. The danger of overlooking early gastric carcinoma masquerading as benign gastric ulcer is real, and even with careful case analysis, including history, initial or serial x-ray examinations, gastric acid estimations, gastroscopy, and cytology, a certain diagnostic error of at least 10% is said to exist.[2,5] However, the final diagnostic test, which is medical treatment with adequate follow-up utilizing all of the diagnostic aids, should make this much lower.[6] Also, of course, there is no operative mortality or morbidity.

The cases for medical trial must be carefully selected, and many patients necessarily should be excluded from consideration. These include those persons with suspicious clinical and/or laboratory evidence of malignancy. From the clinical standpoint the patient with a complicated gastric ulcer (hemorrhage, obstruction, etc.) or in most instances the patient with recurrent ulcer should not be considered a candidate for medical trial. Laboratory studies which contraindicate a medical trial include equivocal x-ray or gastroscopic appearance of the lesion, histamine-fast achlorhydria, persistently positive occult blood in the stool, and positive or suspicious cytologic findings. Also, the patient unable to adhere to a rigid follow-up study, including serial upper gastrointestinal x-rays as well as other appropriate procedures, should not be considered a suitable candidate.

Records of patients with gastric ulcer treated both medically and surgically at the Mason Clinic were reviewed, and the results were compared with the results of other series. This series was obtained by reviewing the records of the x-ray department of the Mason Clinic from the period Jan. 1, 1950, to July 1, 1955. In these years 161 cases were recorded wherein the roentgenologist found a gastric ulcer with no definite evidence of malignancy. All cases of marginal ulcer were excluded, as were those with an obviously ulcerating neoplasm. The records of these patients were reviewed, and follow-up letters were written requesting information essential to this study in those not recently seen. An analy-

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TABLE 1.—*Surgical Indications in Eighty-Eight Cases*

Indication	No. Cases
Possible malignancy	37
Hemorrhage	29
Recurrence or intractability	25
Perforation or penetration	7
Obstruction	5

sis of these cases as to age, sex, size of lesion, level of gastric acidity, etc. was similar to those analyses of other series. Also, the site of these ulcers, with the exception of greater-curvature lesions, has not proved to be of value in differentiating benign and malignant lesions. Similarly, laboratory studies with the exception of histamine-free achlorhydria were not helpful in this differentiation.

Eighty-eight patients (55% of the total cases) were treated surgically. The indications for surgery are outlined in Table 1.

More than one indication was present in a number of patients. Eight malignancies were found out of eighty-eight cases (a 9% incidence). In three of these cases an early malignancy was present in only one edge of an otherwise pathologically benign-appearing ulcer, meeting the pathologic criteria for malignant degeneration in a benign ulcer.[7] This postulate admittedly is not accepted by all. In all malignant cases the x-ray and/or gastroscopic appearance showed no unequivocal evidence of carcinoma, but, when all of the clinical features were analyzed, surgery was mandatory on the basis of a high degree of suspicion of malignancy. The results in this group of 88 surgically treated patients are recorded in Table 2.

The one death occurred in a patient with moderately severe pulmonary emphysema who was operated on because of massive gastrointestinal hemorrhage—the patient died of cerebral anoxia, secondary to prolonged cardiac arrest. There were four patients with moderate dumping symptoms, and in none of these were the symptoms incapacitating. An additional 15 had occasional or mild dumping. Diarrhea was present in seven and in all was slight. Weight loss of over 10 lb. was present in eight of the patients after gastric resection. Considering these figures, the over-all result of surgery was good.

TABLE 2.—*Surgical Mortality and Morbidity Cases*

	Cases	
	No.	%
Mortality	1	1.2
Dumping	4	4.5
Diarrhea	7	8.0
Weight loss (10 lb.)	8	9
Recurrence	1	1.1

Seventy-three patients were treated medically (45% of the total number). The results of treatment are outlined in Table 3.

Twenty-five patients had recurrence of symptoms similar to those which they had when their ulcer was active. X-ray evidence of reactivation of gastric ulceration was not available in all of these persons, but assuming that a return of symptoms meant reactivation of ulcer, the recurrence rate was 34%; of these patients, 6.8% subsequently underwent gastric resection for their continuing problem, and in none of these was malignancy found.

TABLE 3.—*Results in Seventy-Five Medically Treated Cases*

	Cases	
	No.	%
Recurrences	25	34
Deaths	5	6.8
Malignancy?	3	4.1
Not followed	3	4.1
Healed and no recurrence	40	56

Five of the seventy-three patients died. Of these five, two died of other than direct complications of the ulcer or gastric carcinoma. One patient died of carcinoma of the stomach with metastases six months after the initial examination. The two other patients in the group, both with large ulcers, died without the cause of death being established, since it was not possible to follow them and surgery was refused. Assuming that both of these patients had gastric carcinoma, the over-all incidence of carcinoma in the medically treated group would be at the most 4.1%. In the total group of 161

patients, the incidence of carcinoma was 6.8%. Three patients were untraced, but after careful review of their records we would not expect the incidence of carcinoma in these patients to be any higher than that of the whole group. There were 40 patients (55%) with gastric ulcer whose ulcers healed when the patients were given a medical regimen and who have not subsequently presented themselves with symptoms suggestive of reactivation of an ulcer in the follow-up period, which ranges from one and one-half to six years. In most of these cases additional evidence of cure was obtained with subsequent negative x-rays. Therefore, 55% of the medically treated group were well controlled and did not develop recurrent gastric ulcer.

In this series approximately one-fourth of all patients presenting with gastric ulceration did not require surgery; their ulcers healed, and they should continue to do well objectively and subjectively with a medical program. Therefore, this series seems to show that every effort should be made to select carefully cases requiring surgery for the reasons previously listed and to avoid needless resection in those with an ulcer which, with satisfactory treatment, may heal and probably will not recur. The period of study is relatively short, and this group will be followed in order to ascertain the long-range results, i. e., recurrence rate and incidence of carcinoma. Because of the possibility that as many as 5% of patients with gastric ulcer subsequently develop carcinoma of the stomach, anyone with such a lesion should have yearly x-rays of his upper gastrointestinal tract even if asymptomatic.[2]

It is difficult to generalize on the management of uncomplicated recurrent gastric ulcer even if by all the criteria malignancy is improbable. However, in most instances, recurrent gastric ulcer should be regarded as a surgical lesion, not only because of the possibility of carcinoma developing in such a lesion but also because the patient's problem may not be adequately handled by medical means. Furthermore, surgical treatment is usually successful, and operative morbidity and mortality is low. In comparing the figures of this series with those of others in regard to medical treatment, the actual incidence of gastric carcinoma in the medically handled group is low and hardly exceeds the surgical mortality. The recurrence rate is very high in several series, and gastric resection is justified on the basis of this recurrence rate as well as the cancer problem. These comparisons are outlined in Table 4.

TABLE 4.—*Comparison of Figures from This Series with Those of Other Series*

	Mason Clinic, %	Smith et al., %	Swynnerton & Tanner, %	Cain, %
Recurrence or unrelieved symptoms	34	24.9	76.4	79.5
Carcinoma of stomach	4.1	1.7	2.3	10.4

Summary and Conclusions

One hundred sixty-one cases of benign-appearing gastric ulcer are reviewed. Of these, 88 were treated surgically and 73 were given a medical trial. In the surgically treated group the mortality rate was 1.2%. The postoperative incidence of dumping syndrome, diarrhea, weight loss, and recurrence rate was low. Carcinoma was found in eight of the surgically treated group, a 9% incidence. Of the 73 patients given a medical trial, at most 3 (4.1%) were subsequently found to have carcinoma. Forty patients, or 55%, followed one and one-half to six years did not develop recurrent ulcer.

In conclusion, although the surgical treatment of benign-appearing gastric ulcer is good, it seems feasible to treat some cases medically, providing these cases are carefully selected. If such a plan is followed, few carcinomas masquerading as gastric ulcers will be missed. The patient with gastric ulcer which heals medically and does not recur will thereby avoid the risk of gastric resection. If this responsibility is assumed, the patient should be acquainted with the risk of such treatment and the necessity of

a rigid follow-up, which utilizes serial x-rays along with other appropriate procedures.

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Urinary 17-Hydroxycorticoid and Uropepsin Levels with Psychological Data

A Three-Year Study of One Subject

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The rise or fall in urinary 17-hydroxycorticoid levels associated with a pathological increase or decrease in adrenocortical function (such as Cushing's syndrome or Addison's disease) has been well established, and the steroid response to acute physiological and also to psychological stress has been demonstrated.[1-6] There have been few reports, however, concerning the physiological fluctuation of these substances over a relatively prolonged period of time in persons who have no clinically demonstrable endocrine abnormalities.

Research Design

The available biochemical methods for studying adrenocortical activity have been developed so recently that there has not been time to establish a "normal" or "usual" physiological range of fluctuation for a single person. The presently available "limits of normal" are based on the brief sampling of a large number of different persons. Thus any attempt to correlate sustained psychophysiological changes (such as states of nervous tension accompanied by gastrointestinal spasticity) with alterations in relatively constant steroid levels in the same person must depend on long-term observation. The total range of fluctuation in a particular person under varying circumstances in a sense then serves as the base line with which to compare an apparent change during any briefer interval selected for study. Because of individual differences, the same response pattern would not necessarily be found in other subjects. This report of three years of psychophysiological observation of a single patient is presented as a contribution to the methodology of this type of longitudinal investigation. The findings suggest that further research may eventually contribute basic information concerning the homeostatic response of the human organism in health as well as in disease.[7]

The collection of the total output of urine every day over a period of months and years requires special motivation and, since the psychological attitude toward such a demand might actually affect the fluctuation of the biochemical indices under study, it seemed necessary to include consistent evaluation of the patient's conscious and also his unconscious response to the experimental procedure. Because of the patient's desire for psychoanalytic treatment, he was willing to cooperate with daily psychological and

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physiological observation over a period of several years. Psychological study elucidated the unconscious as well as the conscious responses of the patient during alert wakefulness, when asleep and dreaming, throughout all the seasons of the year, and in the course of a wide variety of environmental situations. Above all, the psychoanalytic observation of the patient clarified the development of his attitude toward the urine collections as well as toward the analyst, whom he came to regard as primarily responsible for the conduct of the whole experiment.

Choice of Subject

A young man with a history of ulcer symptoms and an episode of hemorrhage was chosen as the subject for relatively prolonged psychophysiological study because the fluctuations in his emotional state were apparently associated with disturbance of his gastrointestinal function. This seemed to indicate that there might be an especially favorable opportunity to correlate his daily emotional responses with fluctuations in physiological balances as reflected in measurable alterations of the steroid levels. In other words, his constitutional make-up seemed to indicate a type of psychophysiological responsivity favorable for the correlation of physiological and psychological processes. At the time he was chosen it was expected that the research might demonstrate convincing and eventually predictable correlations between certain types of emotional stress from day to day and a rise in the urinary steroid level reflecting increased adrenocortical activity. Although it turned out that certain life experiences could apparently be correlated quite plausibly with changes in the steroid level, the reliability of prediction did not increase to any remarkable extent even after several years of observation. Events concerned with the beginning, the interruption, or the resumption of his visits to the analyst seemed to have a direct effect on his observed biochemical response, but it turned out that this might at times result in a *lowering* of steroid levels and not necessarily a rise. Review of the data after the termination of the period of observation has suggested that the attempt to correlate alterations in the pattern of steroid *variability* with psychological developments has been more successful than the attempt to establish a correspondence between a psychological event and a single or even a series of urinary steroid levels.

Another reason determining the choice of this particular patient for prolonged psychophysiological study was his capacity for careful cooperation in the timing and collection of his urine specimens. The full implication for the patient of this compliance, which he unconsciously experienced as victimization, could not be clearly elicited until after a second hemorrhage, which necessitated a gastrectomy eight months after the termination of the analysis.

Limitations

The fact that he had this hemorrhage even after three years of psychoanalytic treatment emphasizes the question of how much the patient's overcompliance with the experimental situation may have hampered the therapeutic effectiveness of his analysis, although no form of psychotherapy necessarily cures a structural lesion. The hemorrhage constitutes an added warning, at least, for caution concerning the psychological interpretation of the biochemical data. Nonetheless, the clinical findings do seem to provide support for a tentative hypothesis concerning the correlation of homeostatic patterns (as reflected in measurable indices of adrenocortical function) with the changing psychological configuration during the development of a prolonged and relatively intense relationship of the patient to his therapist.

Medical History

Less than a year previous to the period of observation reported here, a married man in his early 30's had tarry stools followed by a hemorrhage severe enough to necessi-

tate a number of transfusions. As indicated above, eight months after the termination of his psychoanalysis he had a recurrence of hemorrhage. This occurred 10 days after making the decision to resign his academic post at a local university and to accept a position of administrative leadership at a smaller college near his boyhood home. Gastrointestinal series subsequent to the initial hemorrhage demonstrated a constant incisura at the apex of the duodenal cap. Later x-ray studies were interpreted as demonstrating chronic peptic ulcer disease of the duodenum without radiological evidence of activity. Subtotal gastrectomy after his second hemorrhage demonstrated superficial erosion of the duodenal mucosa but no evidence of a peptic type of ulceration.

A year before his first hemorrhage he had consulted an internist because of "pressure and bloating" in the midepigastrium three to four hours after eating. These symptoms had developed a few weeks before his oral examinations for a Ph.D. degree, which he anticipated with considerable apprehension. Gastrointestinal series at that time demonstrated an irritable duodenal cap but no crater. The patient requested referral to a psychiatrist.

During eight sessions with the psychiatrist at weekly intervals he talked freely about personal problems and reported considerable anxiety concerning his ability to write a thesis which would please his professor. He described uneasiness about competition with other men and mentioned that when he heard talk about the promotion of his associates he could feel his stomach "turn around and tighten up."

On the eighth visit he announced that he would like to stop coming for a while. In August, two months after breaking off treatment, he had his first hemorrhage, while traveling back to the town where he had lived with his parents until their deaths.

Referral to Psychoanalyst

Late in the following spring (approximately one year after his first eight conferences) he returned to the psychiatrist, asking for help. He had developed what he described as "stomach trouble" while trying to get started on his thesis, which seemed "like a beast" when he found himself alone with it. Self-depreciatory ruminations alternated with "Walter Mitty" daydreams, of which he felt ashamed, about becoming an athletic hero. A comment from his professor indicating that he did not function well as a group member "had hit him hard." He had read about psychoanalysis and wondered if this could provide the cure he needed.

Since his financial resources were limited, he was informed that there would be an opportunity for a standard analysis at a reduced rate if he would be willing to cooperate with a research project involving the daily collection of urine and occasional examinations of his blood. He eagerly consulted the analyst to whom he was referred and expressed the hope that analysis would provide "Elysium behind the mountain," although he said he knew this could not really be true. Remarking that he felt blocked on his thesis, he hoped the analysis would make him more productive.

Preliminary Evaluation

During the three weeks following the initial conference with the analyst, physical examination (including a gastrointestinal series), psychological projection tests, and daily collections of urine, were carried out. Although somewhat overweight for his age and height, he was in good physical health. No clinical or laboratory evidence of abnormality in his adrenocortical function could be demonstrated. Gastrointestinal series indicated that the stomach was high and hypertonic, smooth and flexible in outline, without measurable residue. There was slight tortuosity of the rugae in the antral region but no attendant spasm, and the rugae elsewhere did not appear markedly prominent. The duodenal cap filled and emptied in an irregular fashion, and there was a constant, albeit not marked, deform-

ity, with relative narrowing toward the apex. However, there was no tenderness to direct palpation, and no constant niche or crater could be identified. Duodenal loop and proximal bowel appeared normal.

The initial conference with the analyst had seemed to indicate that the patient could benefit from psychoanalysis. Psychological tests confirmed the analyst's impression that the patient had a certain potentiality for a psychotic type of depression. But he had apparently adapted himself with reasonable success to the demands of college and graduate school as well as to Army service and then to marriage and fatherhood. He seemed capable of sustained emotional investment in the relationship to the therapist. It seemed likely that he could achieve a more comfortable and realistic evaluation of himself and that the resulting improvement in his relationships to other people would have a favorable influence on his family life and on his vocational advancement. The analyst did not consider that the development of a psychosis presented any serious threat. The onset of another dangerous hemorrhage seemed a likelier possibility, especially if the analysis should stir up emotional conflicts affecting his gastrointestinal function.

Methods

Psychoanalysis was then begun and continued for three years, with the usual five sessions a week lasting 50 minutes each. Notes made immediately after each of 593 interviews were kept by the analyst for later correlation with the biochemical findings. Volume, creatinine, urinary 17-hydroxycorticoid, and uropepsin determinations were carried out on daily 24-hour collections of urine (divided into two 12-hour specimens representing the day and the night collections in order to observe a reflection of the diurnal variation). A total of 1168 twelve-hour specimens was examined before, during, and after the analysis. When, as sometimes happened, the patient collected only a 12-hour specimen instead of two specimens representing the total 24-hour output, the biochemical determinations were carried out, but only those specimens representing half of a total 24-hour collection have been reported here (about 740 twelve-hour specimens).

Urinary 17-Hydroxycorticoids.—These were measured by the method of Reddy Jenkins, and Thorn.[8] Normal values for this method range from 1 to 10 mg. per 24 hours for a young man. The laboratory error for this method is less than 1 mg. The determination includes the major metabolic products of hydrocortisone (Compound F), the principal glucocorticoid secreted by the human adrenal cortex. Unlike previous methods, it detects glucocorticoid metabolites in the conjugated as well as in the free form. In contrast to blood steroid determinations, which reflect the steroid level at any given moment, the urinary method indicates the total quantity of the accumulated products resulting from adrenal cortical activity over a 12- or 24-hour period of collection.

Uropepsin.—Since the patient had a history of ulcer, uropepsin determinations were carried out as an index of gastric activity. The stomach is responsive to nervous as well as to humoral influences, of course, but adrenal cortical activity at least contributes a "permissive" factor to gastric secretion.[9]

The uropepsin level was determined by a modification of the methods described by Bucher[10] and by Anson and Mirsky.[11] Results are reported in terms of units per 12 or per 24 hours. The range of values for this determination in a series of healthy young males under the ordinary stress of college work has been 1500 to 8000 units per 24 hours at this laboratory. The range of laboratory error for the method has been found to be ±10%.

Creatinine Excretion.—This was measured by Folin's method as modified by Lambert.[12] Results are expressed in milligrams per 24 hours.

Statistical Methods.—Statistical methods included determination of means, standard deviations, and coefficients of variation and correlation. The mean values helped to summarize the findings over a segment of time as a basis for comparison with a period of equal duration later in the course of observation. The coefficient of variation (the standard deviation for each six-month period divided by the mean for that period) indicated the range of dispersion of the values obtained during a period of time. This statistical method has the advantage of converting absolute dispersions to a percentage score, which gives the relative dispersion of any series and is independent of the units of measurement. Coefficients of correlation were done by the product-moment method. A time series for biweekly 17-hydroxycorticoid means indicated the general trend. This helped to correct for a certain distortion of the findings which might have resulted from arbitrary divisions of the data into six-month intervals, which obliterate the time sequence within the six-month section of observation.

TABLE 1.—*Statistical Data for 17-Hydroxycorticoids, Uropepsin, Creatinine, and Total Volume During Three Years of Psychoanalysis* *

		Year I		Year II		Year III	
		1st 6 Mo.	2d 6 Mo.	1st 6 Mo.	2d 6 Mo.	1st 6 Mo.	2d 6 Mo. †
		N=43	*N*=94	*N*=79	*N*=71	*N*=53	*N*=66
24-hr. 17-OH	$\bar{M}$	8.02	10.58	10.10	9.28	8.74	7.22
	SD	3.28	2.70	3.12	2.51	1.96	2.57
	V	41	26	31	27	22	36
		N=55	*N*=113	*N*=96	*N*=82	*N*=59	*N*=75
12-hr. 17-OH (day)	$\bar{M}$	5.14	6.68	5.84	5.38	5.18	4.11
	SD	2.14	1.69	2.40	2.02	1.41	1.53
	V	42	25	41	37	27	37
		N=106	*N*=124	*N*=126	*N*=115	*N*=89	*N*=104
12-hr. 17-OH (night)	$\bar{M}$	2.39	3.80	3.98	3.79	3.55	2.90
	SD	1.66	1.55	1.92	1.22	1.09	1.07
	V	69	41	48	32	31	37
		N=43	*N*=94	*N*=79	*N*=71	*N*=53	*N*=66
17-OH excretion (night), %	$\bar{M}$ (%)	34	35	41	43	40	43
	SD	16	9.6	12	11	8	11.9
	V	47	27	29	26	20	28
		N=41	*N*=92	*N*=77	*N*=49	*N*=47	*N*=63
24 hr. Uropepsin	$\bar{M}$	11,051	10,805	11,360	11,545	10,491	12,338
	SD	1,733	2,105	2,376	2,033	1,788	3,496
	V	16	19	21	18	17	28
		N=52	*N*=116	*N*=92	*N*=63	*N*=53	*N*=72
12-hr. uropepsin (day)	$\bar{M}$	6,336	6,006	6,293	6,392	5,628	6,726
	SD	1,203	904	1,572	1,585	1,496	2,283
	V	19	15	25	25	27	34
		N=99	*N*=125	*N*=121	*N*=109	*N*=82	*N*=103
12-hr. uropepsin (night)	$\bar{M}$	5,062	4,783	4,960	5,162	4,695	5,672
	SD	1,076	964	1,448	1,295	1,119	2,153
	V	21	16	29	25	24	38
		N=45	*N*=93	*N*=77	*N*=71	*N*=53	*N*=66
24-hr. creatinine	$\bar{M}$	2,168	2,218	2,175	2,181	2,268	2,333
	SD	224	242	375	285	158	401
	V	10	11	17	13	7	17
		N=47	*N*=96	*N*=80	*N*=73	*N*=53	*N*=66
24-hr. total volume	$\bar{M}$	2,525	2,837	3,043	2,565	2,680	2,180
	SD	592	545	611	519	548	401
	V	23	19	20	20	20	18

* 17-OH indicates 17-hydroxycorticoids; $\bar{M}$, mean; SD, standard deviation; V, coefficient of variation.
† See Table 2 for breakdown of 2d 6 mo. of Year 3.

Findings (Tables 1 and 2)

A. Twenty-Four-Hour Urinary 17-Hydroxycorticoid Levels.—1. Mean Values: The mean values of the 24-hour urinary 17-hydroxycorticoids rose from 8.02 mg. during the first six months to 10.58 mg. during the second six months (significant at between the 0.02 and 0.01 level of probability). Many individual determinations during the second and third six-month intervals were over 14 mg. (there were several between 16 mg. and 18 mg.), indicating a type of 17-hydroxycorticoid excretion comparable to levels usually found in Cushing's syndrome of moderate severity. During the succeeding six-month intervals the mean values for 24-hour 17-hydroxycorticoid levels fell steadily (10.10, 9.28, 8.74, 7.22 mg.). During the final year there were scarcely any individual determinations over 12 mg. (The mean values fell even further, to 5.04 mg. during the third and fourth months after termination of the daily psychological observations.) A time series for biweekly 24-hour 17-hydroxycorticoid means demonstrated a similar general trend (Fig. 1). The curve rose to comparatively high levels during the second six months of the first year and the first six months of the second year. There was a definite downward trend throughout the final year of observation. Although these outstanding characteristics of the curve closely corresponded to the trends indicated by the mean values for each six-month period, the biweekly time series brought out a difference during the second six months of the second year. The downward trend of the first three months (of this six-month

TABLE 2.—*Breakdown of Statistical Data for Final Six Months of Psychoanalysis* *

		1st 3 Mo.	2d 3 Mo.
		N=37	*N*=29
24-Hr. 17-OH	$\bar{M}$	7.42	6.96
	SD	1.75	3.32
	V	24	48
		N=43	*N*=32
12-hr. 17-OH (day)	$\bar{M}$	4.40	3.71
	SD	1.42	1.60
	V	32	43
		N=57	*N*=47
12-hr. 17-OH (night)	$\bar{M}$	3.03	2.75
	SD	0.99	1.11
	V	33	40
		N=37	*N*=29
17-OH excretion (night), %	$\bar{M}$ (%)	43	43
	SD	10.5	13.4
	V	24	31
		N=36	*N*=27
24-hr. uropepsin	$\bar{M}$	10,339	15,000
	SD	2,603	3,425
	V	25	23
		N=43	*N*=29
12-hr. uropepsin (day)	$\bar{M}$	5,821	8,069
	SD	1,482	2,165
	V	25	27
		N=56	*N*=47
12-hr. uropepsin (night)	$\bar{M}$	4,648	6,891
	SD	1,120	2,646
	V	25	38
		N=37	*N*=29
24-hr. creatinine	$\bar{M}$	2,388	2,263
	SD	429	353
	V	17	16
		N=37	*N*=29
24-hr. total volume	$\bar{M}$	2,223	2,127
	SD	372	432
	V	17	20

* 17-OH indicates 17-hydroxycorticoids; $\bar{M}$, mean; SD, standard deviation; V, coefficient of variation.

period) was shown to be reversed during the succeeding three months.

2. High and Low Values: As indicated above, there were many 24-hour urinary 17-hydroxycorticoid values above what is usually considered average for a young man with normal adrenocortical function (especially during the second six months of the first year and the first six months of the second year). There were also a number of comparatively low values. Most of these occurred during the first six months of observation.

Inspection of a chart graphing each individual determination for the whole three-year period of observation seemed to indicate that a trend toward comparatively high or comparatively low values could be emphasized by the percentage of the total number of values above 12 mg. and under 6 mg. for each six months during the three years of observation. These values seemed to represent excretion rates outside the ordinary range of fluctuation for this patient (Fig. 2). (The limits of 12 mg. and 6 mg. roughly corresponded to the limits of the standard deviation for the total series. The values for the total three-year period were found to be normally distributed about a mean of 9.20. Standard deviation was 2.97.)

This type of consideration emphasized certain trends which had already emerged from tabulation of the means for each six-month period. The percentage of unusually high values increased during the second and even more during the third six-month periods (16.3% during the first six months, 26.6% and 30.4% during the second and third six-month periods). The percentage of unusually high values fell steadily during the subsequent six-month periods of observation (15.5%, 3.8%, and 1.5%). The comparatively low values, relatively numerous during the first six months (32.6

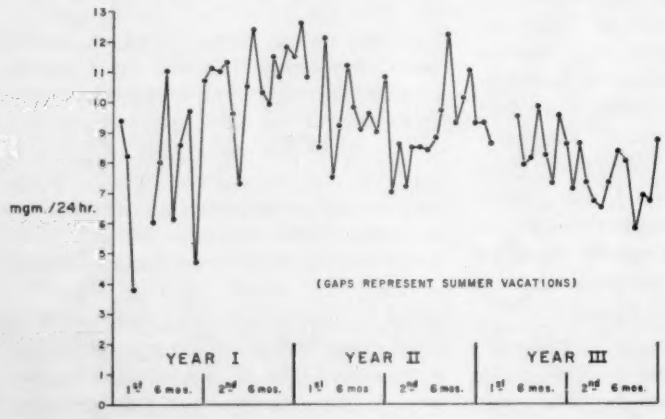

Fig. 1. — Time series for biweekly 24-hour urinary 17-hydroxycorticoid means during three years of psychoanalysis.

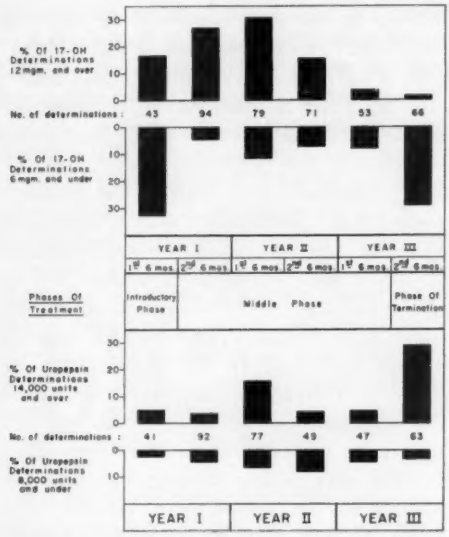
% Of 17-OH Determinations 12mgm. and over
No. of determinations: 43 94 79 71 53 66
% Of 17-OH Determinations 6mgm. and under
YEAR I
YEAR II
YEAR III
1st 6 mos. 2nd 6 mos. 1st 6 mos. 2nd 6 mos. 1st 6 mos. 2nd 6 mos.
Phases Of Treatment
Introductory Phase
Middle Phase
Phase Of Termination
% Of Uropepsin Determinations 14,000 units and over
No. of determinations: 41 92 77 49 47 63
% Of Uropepsin Determinations 8,000 units and under
YEAR I
YEAR II
YEAR III

Fig. 2.—Percentage of high and of relatively low 17-hydroxycorticoid and uropepsin values, with phases of the treatment during three years of psychoanalysis.

mg.) were much fewer during the subsequent six-month periods of observation (4.3, 11.4, 7.0, and 7.5 mg.) until the final six months (28.8 mg.), at which time, however, the abnormally high values had almost completely dropped out.

3. Coefficient of Variation: The time series for biweekly 24-hour 17-hydroxycorticoid means (Fig. 1) indicated that the widest fluctuation occurred during the early months of observation and that, especially during the final year, there was a damping of these fluctuations corresponding to the decline in the coefficient of variation. This trend was moderately reversed during the final two to three months.

B. Twelve-Hour Urinary 17-Hydroxycorticoids (Daytime and Nighttime Output).

1. Mean and Individual Values: The specimens were divided into 7 a. m. to 7 p. m. and 7 p. m. to 7 a. m. portions. The mean of the daytime output of 17-hydroxycorticoids was greater than the nighttime output throughout the period of observation (Fig. 3). (At this hospital, laboratory studies on diurnal variation demonstrate a mean of 69% excretion during the day and 31% at night.) The curve for the nighttime output (for each six months) in this patient paralleled the curve for the daytime output. On certain nights, however, the nighttime output was greater than during the daytime, and for the entire period of this study 39% of the 24-hour total was excreted during the nighttime.

2. Coefficient of Variation: During the course of the observations there was a tendency for the coefficient of variation to equalize for nighttime and daytime values, and during the final six months they were exactly the same (Fig. 3).

C. Twenty-Four-Hour Uropepsin.—1. Mean Values: The mean values for the

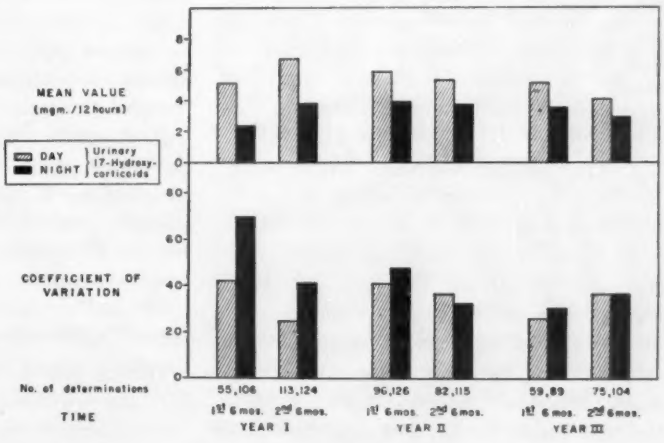

Fig. 3.—Daytime and nighttime urinary 17-hydroxycorticoid levels for each six-month period during three years of psychoanalysis (mean value and coefficient of variation).

24-hour uropepsin for each period of six months were above 10,000 units throughout the period of observation. The grand mean was 11,268 (standard deviation of 2398). This level is typical of patients with duodenal ulcer. The mean for the final six months was higher than for any corresponding period during the three years of observation (12,338 compared to 10,491 during the preceding six months). Most of this rise took place during the final three months (10,339 during the first three months and 15,000 during the final three months). During the third and fourth months after termination of daily observations, the mean values for uropepsin again fell to the relatively nonfluctuating but comparatively elevated levels which were characteristic for the whole period of observation.

2. High and Low Values: Percentage of total number of 24-hour uropepsin values above 14,000 units and below 8000 units for each six-month period was determined in the same manner as had been done for the 17-hydroxycorticoids. (These limits of 14,000 and 8000 again corresponded to the limits of ±1 standard deviation for the total series; Fig. 2).

As indicated, there was a sharp rise in the abnormally high uropepsin values during the final six months of daily observation (the percentage of 24-hour uropepsin values above 14,000 during the first six months of the final year was 4.3% and rose to 28.6% during the final three months). There had been an earlier but much less significant rise in the percentage of 24-hour uropepsin values above 14,000 units during the first six months of the second year (15.6%).

3. Coefficient of Variation: Coefficient of variation for 24-hour uropepsin was at its highest during the final six months (28).

D. Twelve-Hour Uropepsin Values (Daytime and Nighttime Output).—1. Mean Values: The mean of the daytime output of uropepsin was significantly greater than the output during the night. The ratio for the whole period of observation was 55% of the total during the day and 45% during the night. On some occasions the output during the night was greater than during the day.

2. Coefficient of Variation: No significant difference in coefficient of variation for the day and night output could be demonstrated.

E. Comparison of Curves for Twenty-Four-Hour Uropepsin and 17-Hydroxycorticoid Excretion.—1. Mean Values: Attempts were made to correlate 24-hour uropepsin and 17-hydroxycorticoid values for each six-month period (with the final six months broken down into three-month intervals). During the first year, the day-to-day correlation of 17-hydroxycorticoid and uropepsin was not statistically significant (−0.06 and 0.01). During the first six months of the second year, on the other hand, 17-hydroxycorticoids and uropepsin showed a significant positive correlation (0.27). During the second six months of the second year and the first six months of the final year, no significant correlation could be demonstrated (−0.11 and 0.21). During the final six months of the third year, however, a significant negative correlation could be demonstrated (−0.25, which is significant at better than the 0.05 level). A breakdown into three-month intervals indicates that it is again the last three months that are most crucial. (By three-month periods the correlations are 0.02 and −0.40 at the 0.05 level of significance.) Thus correlations for only two periods are statistically significant, the first six months of the second year (0.27) and the final six months of the analysis (−0.25), primarily the final three months (−0.40).

2. Coefficient of Variation: Throughout the period of observation the coefficient of variation for 17-hydroxycorticoids was considerably higher than for uropepsin (32 for the 17-hydroxycorticoid and 21 for the uropepsin).

Psychological Interpretation

During the preliminary evaluation (before the beginning of the psychoanalysis), steroid studies on a week of daily urine

collections showed a steady pattern well within the normal range, with about two-thirds of the substance excreted during the day and one-third, at night. On the night after the patient had his first analytic session, however, this proportion was reversed (i. e., he excreted much more of the substance during the night following his first 50 minutes on the couch than during the preceding day). Throughout the analysis the nights when the nighttime output was greater than during the day seemed to correspond to the emergence of disturbing impulses, and he often reported dreams of an anxious type on the day following a night when the steroid level had been relatively high.

Review of the notes made after each of the interviews indicates that this psychoanalysis, like most others, seemed to evolve through successive phases. There was, of course, considerable overlapping of these phases, and brief characterization greatly oversimplifies the complexity of the treatment process.

I. Introductory Phase.—During the introductory phase the patient was outwardly almost overly cooperative, but he also manifested a certain wariness about allowing himself to become too much emotionally involved in his relationship to the analyst. This corresponded to rapid fluctuations from unusually high to relatively low 17-hydroxycorticoid levels during the first six months.

II. Middle Phase.—This was succeeded by the middle phase, lasting over two years, during which he allowed himself to become emotionally very much committed to the treatment process. This phase was ushered in by the emergence (during the second six months of the first year) of a close attachment to the analyst, during which he relived many of the emotional experiences of his childhood, including feelings of affection but also of shame and guilt. The months when this attachment was most prominent corresponded to well-maintained and unusually high 17-hydroxycorticoid levels ordinarily found in patients with Cushing's syndrome.

During the first six months of the second year his close attachment continued but he also became somewhat rebellious, occasionally neglecting to collect urine samples, and then reacted with intense feelings of guilt. This corresponded to the maintenance of relatively high steroid levels and, for the first and only time, a corresponding rise in the mean levels of uropepsin. The rebellion and guilt gradually diminished, and his capacity for a genuine (in contrast to a merely propitiatory) working alliance became more evident. His relationship to his colleagues improved, and he made good progress on his doctor's thesis, which he successfully completed during the later months of his analysis. During this period, which lasted from the middle of the second year until the final months of treatment, the mean values for 17-hydroxycorticoids fell steadily (except for a peak two to three months before the end of the second year, which exactly corresponded to the patient's consideration and final refusal of an academic position actually offered to him in a distant area, which would have necessitated termination of his analysis; his acceptance of a position from the same university eight months after the termination of the analysis immediately preceded the hemorrhage which led to his gastrectomy). A mathematician, who knew nothing about the analysis, described the curve for the biweekly time series (Fig. 1) as showing a progressive damping down of the fluctuations. This seemed to correspond to the analyst's impression that the patient was beginning to improve. When, toward the end of the third year, the patient asked his wife whether she thought he had changed in any way since beginning the analysis, she answered that he seemed a lot "steadier."

III. Phase of Termination.—During the last six months of the analysis, and especially during the final three months, the patient was keenly aware of the imminent termination of his treatment. He was

anxiously preoccupied with doubts as to whether he had obtained enough additional strength to make up for his sense of personal inadequacy. The emotional implications of losing the close relationship to the analyst, however, were shut out of his mind to a large extent, and there was even a slight tendency toward euphoria. This psychological defense seemed to correspond to a sharp increase in the proportion of low 17-hydroxycorticoid values, comparable to the situation during the first six months of the analysis except for the absence now of the high individual values which had characterized the introductory phase. This pattern corresponded in some ways to the abnormally low excretion of glucocorticoids, reported elsewhere, in a manic-depressive patient during the months of manic overactivity.[2] The sharp rise in uropepsin values during the terminal phase of the analysis seems to accord with Mirsky's [13] suggestion that an increase in the uropepsin excretion rate occurs in response to life situations which appear to threaten or to mobilize "the individual's unconscious wishes for love and to be taken care of." Margolin [14] directly observed alterations in the response pattern of gastric secretion during phases in the psychoanalysis of a woman with a gastric fistula. Engel's [15] recent study of an infant with a fistula suggested that early maternal deprivation (of which this patient's early history gave abundant evidence) may influence patterns of gastric response. In this patient the persistence of an unusually high plateau of uropepsin excretion throughout his analysis and also after its termination may correspond to his constitutional make-up.[16,17]

IV. Post-Treatment Phase.—He came in for occasional reports during the months after the conclusion of his analysis and seemed to be doing well. The mild euphoria, however, continued, and he seemed perhaps overly eager to present himself as a person who had been successfully analyzed rather than to bring up difficulties or disappointments.

During the months immediately following termination of the analysis, the uropepsin values fell from the peak in the final months of the analysis to the comparatively elevated plateau characteristic for the whole period of observation. The downward trend of the 17-hydroxycorticoids characteristic of the last 18 months of the analysis continued.

Repetition of projection tests by the psychologist indicated that he had become more assertive, more expressive (change in color ratio from 11 form-color:5 color-form to 5 form-color:10 color-form on the Rorschach), and less inhibited by preoccupation with his own phantasies. Indications of the potentiality for psychosis had now entirely disappeared. It appeared, however, as though certain neurotic anxieties had not yet been fully resolved. Changes in the number of his responses and his reaction time suggested an increase in intellectual efficiency. His response time previous to analysis had been erratic (ranging from 2 to 45 seconds), but now the fluctuation was not so wide (ranging from 3 to 10 seconds).

Gastrointestinal Hemorrhage

Eight months after termination of the analysis the patient was faced with a decision involving the assumption of responsible leadership, which also required moving away from the part of the country where his analyst lived. He showed evidence of emotional turmoil and wanted advice from the analyst but made it clear that he would resent it if the analyst offered any, as he wished to make the decision himself, regarding it as a test of his courage and emotional maturity. Ten days after deciding to accept the new opportunity he had a severe hemorrhage, necessitating gastrectomy, which, however, demonstrated only superficial erosion of the duodenal mucosa. From a psychological point of view, it seemed evident that his defenses had given way under the impact of actual promotion and real separation.

Whether the inner capacities for self-stabilization activated by psychoanalytic

treatment would eventually have resulted in permanent remission of his gastrointestinal malfunction and perhaps even a lowering of his uropepsin levels could only have been answered several years later. During interviews following the gastrectomy, from which he made a rapid recovery without complications, he was able to express his resentment toward the analyst more directly than at any previous time. This had to be encouraged, however, and he was never able fully to overcome his inhibitions concerning the direct expression of hostile impulses. He was, however, able to take over the new position, and his personal development during future years will demonstrate the extent to which he has actually made the genuine gain, perceived by the analyst, in his emotional flexibility.

Comment

Recent studies have been reported of gastric and adrenal activity in normal subjects before and after stimulation with corticotropin.[18-21] Although after stimulation with corticotropin gastric peptic secretory activity came more directly under adrenal dominance, it was demonstrated that in the absence of exogenous pharmacological stimulation the stomach acts semiautonomously relative to the adrenal cortex. The absence of day-to-day correlations of uropepsin and 17-hydroxycorticoid levels during most of the observation made on this patient confirms these findings. During the first six months of the second year, however, during a stormy phase of his analysis, the correlation was positive. During the final three months of the analysis the correlation was significantly negative (that is, the uropepsin curve rose sharply, whereas the curve for 24-hour 17-hydroxycorticoid values continued to fall).

No peptic ulcer could be demonstrated by careful microscopic sections following total gastrectomy. On the other hand, gastrointestinal ulcerations of a superficial type have been observed during acute adrenal crises in humans.[9] Furthermore, superficial ulceration with massive hemorrhage has been reported in patients who developed ulceration in response to the administration of adrenal steroids.[22-24] Some of these ulcerations were of the chronic duodenal or gastric type, but others were superficial, as demonstrated histologically in the duodenum of this patient. Moreover, adrenal hyperplasia has been reported in 14% of a series of patients with acute superficial gastric or duodenal ulceration.[25] This patient's 24-hour 17-hydroxycorticoid values immediately after his second hemorrhage were relatively high (17.3, 10.3, and 11.9 mg. on successive days). The rise at this time of the 17-hydroxycorticoids to levels characteristic of the most stormy months of his treatment suggests a relationship between his adrenocortical function and the pathological gastric response similar to the ulceration, perforation, or dangerous hemorrhage occurring as a complication following administration of adrenal steroids to patients with a high level of uropepsin excretion.

Summary

Daily observations of urinary 17-hydroxycorticoid levels, uropepsin, creatinine and volume were carried out on a single person for a period of three years.

Psychological observation during daily psychoanalytic sessions helped to elucidate the unconscious as well as the conscious responses of the patient to daily happenings, and especially to the experimental procedure, including not only the urine collections but also the analytic observer.

Statistical methods included determinations of means, standard deviation, and coefficients of variation and correlation. A time series for biweekly 17-hydroxycorticoid means helped to correct for distortion of the findings resulting from arbitrary division of the data into six-month intervals for convenient comparison.

Twenty-four-hour 17-hydroxycorticoid levels rose significantly after the first six months, with many individual determinations over 14 mg., comparable to levels

found in Cushing's syndrome of moderate severity. During the last 18 months of observation these levels fell steadily and there was a striking damping of fluctuations in contrast to the variability during the initial months of observation.

The 24-hour total was divided into two 12-hour specimens representing the output during the day and during the night. The mean of the daytime output of 17-hydroxycorticoids was greater than the nighttime output, with certain exceptions corresponding to the emergence of disturbing thoughts and impulses during the course of the patient's psychoanalytic treatment.

Since the patient had a history suggesting ulcer (including a gastrointestinal hemorrhage), uropepsin determinations were carried out as an indication of gastric activity. The mean values throughout the period of observation were above 10,000 units, a level often found in patients with duodenal ulcer. The mean value rose sharply to 15,000 units during the final three months of observation, when the patient was anxiously anticipating the termination of treatment, although the 17-hydroxycorticoid level continued to fall.

The biochemical findings have been interpreted as providing support for a tentative hypothesis concerning the correlation of homeostatic patterns (as reflected in measurable indices of adrenocortical function) with the changing psychological configuration during the introductory phase, the middle phase, and the phase of termination in a prolonged and relatively intense relationship of the patient to his therapist.

A severe hemorrhage eight months after the termination of psychoanalytic treatment necessitated a gastrectomy which demonstrated only superficial ulceration of the duodenal mucosa. The hemorrhage occurred 10 days after the patient decided to accept a vocational promotion involving greatly increased responsibility and geographical separation from his therapist. This emphasized the question of how much the patient's overcompliance with the experimental situation may have hampered the therapeutic effectiveness of his psychoanalysis, although he made a prompt recovery from the gastrectomy, was able to take over his new position, and in general showed evidence of significant psychological improvement.

Conclusion

Daily observation of urinary steroids and uropepsin with concurrent psychological study of a person over a period of three years has given support to certain tentative hypotheses concerning the correlation of disturbances in relatively constant biochemical and psychological homeostatic balances and defensive equilibria.

Dr. I. Herbert Scheinberg, Dr. Sanford Gifford, Dr. Eugene C. Eppinger, Dr. Thomas W. Botsford, Dr. Gustave J. Dammin, and Dr. James B. Dealy Jr. cooperated in the treatment and study of this patient, and the staff members of the Metabolic and Gastrointestinal Laboratories at the Peter Bent Brigham Hospital gave technical assistance. Dr. Anthony F. Bartholomay gave advice concerning presentation of the statistical findings.

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The Concept of Early Diagnosis in Strokes

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Cerebrovascular disease remains as an important medical problem. Cerebral infarction is the common variety and, when extensive, defies adequate treatment or functional replacement. Prevention of such damage to the brain would be one approach to this serious problem. In the absence of specific measures for the prevention of cerebral atherosclerosis, attention need be drawn to means that can be utilized to anticipate and thereby possibly prevent the occurrence of selected varieties of strokes. The purpose of the present paper is to discuss certain early symptoms, their pattern and their significance, and their role in this early recognition. Thus, in carefully chosen instances of cerebrovascular disease, treatment might be instituted prior to the development of massive cerebral damage. A report on a method of treatment with use of anticoagulant drugs in these symptom-complexes has been given elsewhere.[1]

The differential diagnosis of the three commonest types of cerebrovascular disease —thrombosis, embolism, and hemorrhage— must be made, if possible, in all instances. The sudden occurrence of headache, massive neurologic signs, coma, and bloody cerebrospinal fluid in a hypertensive person indicates an intracerebral hemorrhage, while the equally sudden appearance of neurologic signs in a person harboring a known source for emboli, such as lesions of bacterial endocarditis, suggests cerebral embolism. Although these two conditions must be recognized, our discussion will be limited to the commonest condition—that of focal cerebral ischemia or infarction (commonly referred to as thrombosis), which accounts for some 80% of all strokes.

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Many clinical syndromes have been delineated, the nature of the syndromes depending on which cerebral vessel is occluded. These are well known and will be dealt with only insofar as is necessary to illustrate the concepts to be discussed. It is important to note, however, that continued study has indicated that there are even more important differences among various types of strokes than just their anatomic location. In some studies concerned with these various syndromes, previous or prodromal symptoms have been tabulated in retrospect, but little or no attention has been attached to these symptoms per se from the standpoint of diagnosis prior to the fact of actual thrombosis of a vessel. These episodes of neurologic abnormality, often referred to as vasospastic phenomena, are common. In many instances such attacks may form a pattern which permits the establishment of a diagnosis of intermittent insufficiency of blood flow within the field of a particular artery. The particular importance of this state of insufficiency is that it may be a forewarning of occlusion of a major vessel with resulting cerebral infarction. Prevention of such occlusion and infarction is the ultimate goal in treatment.

The Syndrome of Intermittent Insufficiency of the Vertebral-Basilar Arterial System

The basilar artery and its diverging terminal branches, the posterior cerebral arteries, vascularize the pons and upper part of the brain stem, the superior portion of the cerebellum, the posterior thalamus, the basal portions of the temporal lobes, and

the calcarine (visual) area of the occipital lobes. If the vertebral arteries, whose junction forms the basilar, are included, the field of supply is broadened to include all structures in the posterior cranial fossa. The structures thus supplied by the vertebral and basilar arteries and their ramifications are many, and the functions subserved are complex. Correspondingly, the symptoms produced by deficient blood supply will vary, depending on the particular area involved.

In three studies [2-4] on occlusion of the basilar artery, it was found that from 40% to 70% of the patients had had previous transitory symptoms. It seems likely, therefore, that a diagnosis of intermittent insufficiency within this vascular bed can be made in many instances, and the presumption would be that some subjects, at least, would later sustain thrombosis of the basilar artery or its branches.

The syndrome of intermittent insufficiency of the vertebral-basilar arterial system [4-6] consists of sharply episodic attacks of visual dimness, weakness of the limbs (monoparesis, hemiparesis, quadriparesis), dysarthria, dysphagia, diplopia, confusion, and vertigo in various combinations. Between attacks the patient is well and the neurologic examination reveals normal findings. During an attack, appropriate neurologic abnormalities are present.

A single episode may suggest the diagnosis if it includes most or all of these symptoms. Usually, however, a single episode is a fragment of the whole, and one can only suspect the diagnosis. It is when a group of these episodes, clearly delineated by the patient, occurs over weeks or months with the inclusion of most of the abovementioned symptoms that one can be more certain of the diagnosis. In all instances, careful study need be made to determine that intermittent vascular insufficiency is the fundamental factor involved, rather than some other cause, such as an expanding intracranial mass or epilepsy.

Certain complaints are highly suggestive: decrease in vision or anopsia in both halves of the visual field, that is, bilateral homonymous hemianopsia [7]; alternating hemiparesis, that is, hemiparesis involving sometimes the right limbs, sometimes the left; dysarthria (not aphasia) and dysphagia, and diplopia. Particularly, their occurrence together is characteristic.

In addition, certain other symptoms may be seen which, if associated with the abovementioned symptoms, take on additional significance. Vertigo is a very common symptom in these patients, but it is also a common and often ill-defined symptom anyway. Thus, episodes of vertigo alone, while possibly due to basilar insufficiency, certainly are not diagnostic. The symptom of vertigo should be limited to the sensation of rotation, thus eliminating such feelings described as "lightheadedness," "giddiness," "floating," and "dizziness." Dizziness is often mentioned by these patients, but used alone it is of limited value in diagnosis. Tinnitus and loss of hearing are rarely part of this syndrome and must first be considered to arise from other causes, such as Ménière's syndrome, lesions of the cerebellopontine angle, or possibly aneurysm of the basilar artery.[8] Periods of confusion or faintness and numbness often occur but in themselves are in no way characteristic. They are important adjuncts, however, particularly if sharply episodic and clearly described by the patient or an observer. Numbness must be well localized, and when it alternates from side to side in separate episodes it is highly suggestive of insufficiency within this system.

Though headache may occur, it is usually too vague to be of value as a diagnostic point; since it may be of importance for the diagnosis of a mass lesion, it seems best to consider it in this way. Unilateral blindness probably never occurs.

The diagnosis, then, depends on sharply episodic attacks of clearly defined symptoms, the pattern of which can be considered to be the result of intermittent insufficiency of blood flow in the vertebral-basilar arterial system. The diagnosis is difficult or

impossible to make along the fringes of the syndrome. It may even be incorrect. It would seem wise at the present time to be restrictive in making the diagnosis. Because the diagnosis rests entirely on the history, unless an attack is observed, careful questioning is essential to obtain an accurate description from the patient. It cannot be overemphasized that these individual complaints may result from many other illnesses.

Ancillary studies, such as roentgenographic examination of the skull, electroencephalographic examination, and examination of the spinal fluid, may be needed to aid in the exclusion of other causes for the complaints. The x-ray appearance of the skull and the cerebrospinal fluid should be normal. The electroencephalographic examination between attacks gives normal results or presents evidence of minimal nonspecific dysrhythmia. The visual fields are normal between attacks. Choked disks of increased intracranial pressure are not seen. Pneumoencephalographic examination may have to be done. Cerebral angiography, especially through the vertebral arteries, probably is best avoided, since the risks from this procedure are increased if cerebrovascular disease is present. In fact, Sugar and Bucy [9] reported on three patients with homonymous hemianopsia as the only abnormality noted on neurologic examination in which they did vertebral arteriography. The angiograms showed severe arteriosclerosis of the vertebral-basilar system, and two of the patients died soon after the procedure.

The various convulsive phenomena need be considered in differential diagnosis. In general, the quality of the dysfunction in such phenomena is different. Episodes of complete unconsciousness, often a prominent feature in convulsive disorders, appear to be uncommon in transitory insufficiency of the basilar artery. Furthermore, convulsive disorders are more rapid in their appearance, often last a briefer period, and may be associated with such typical feature as auras and clonic movements. Dysphagia and diplopia are uncommon in convulsive disorders.

Expanding mass lesions tend to cause progression of symptoms. Evidence of increased intracranial pressure, such as headache and choked disks, together with certain persisting neurologic abnormalities, is frequently present. Roentgenograms of the skull may show appropriate abnormalities.

Illustrative Cases

Case 1.—A 72-year-old man came for medical attention on Sept. 23, 1936, because of headache, dizziness, and speech trouble. Eleven days previously he felt "dizzy and weak," objects whirled about him, and he staggered as he walked. In a few seconds his vision was dim, his speech slurred, and he could not move his tongue. In 5 minutes he was improved and able to eat, although mild vertigo persisted for 30 minutes. He had three similar attacks on the day before he came for medical attention, all consisting of vertigo, blurring of vision, and weakness in the extremities; in two he was also anarthric. On several occasions he had diplopia alone.

Neurologic examination revealed normal findings except for small pupils, questionable nystagmus on upward gaze, and nystagmus on lateral gazes. The spinal fluid was normal. During the next few days he had one attack like those described and several separate episodes during which he was confused for 10 to 15 minutes.

On Oct. 14, 1936, when he awakened, his right limbs and the lower half of the right side of the face were weak. In an hour these limbs were paralyzed. Examination also disclosed his vision to be markedly decreased, speech slurred, and swallowing impaired. He quickly became stuporous, although he could be aroused. The following day his left side was weak and he became comatose. His temperature gradually rose, and it was 107 F when he died, on Oct. 19. Necropsy revealed thrombosis of the basilar artery and infarction of the pons.

This man suffered five transient episodes, consisting variously of weakness of the limbs, vertigo, poor vision, and anarthria. He was symptomless between them. Diplopia occurred on several other occasions. This phase would constitute the syndrome of intermittent insufficiency of the vertebral-basilar arterial system. But soon the pattern changed and neurologic abnormalities persisted. The findings at necropsy strongly

imply that these symptoms and signs were related to occlusive disease within this arterial system.

CASE 2.—A 59-year-old man, hospitalized for treatment of arthropathy, experienced the sudden onset of vertigo, numbness that began in the forehead and quickly involved the upper and then the lower limbs, diplopia, and a faint feeling. Within a few minutes, weakness in his four limbs, slurred speech, and profuse perspiration gradually developed. He was observed at this time, and it was noted that his words were well chosen but the speech was "mushy" and that he could not lift the bed covers. He had blurred vision but no diplopia, for he could not move his eyes to either side, and on attempted upward gaze a vertical nystagmus was seen. The pupils were equal. In 30 minutes he began to regain normal feeling, and within 2 hours he was normal.

Some two weeks later,* there was a period of several days during which his vision was blurred and he had episodic hiccups. Then, over a period of three days, he experienced, successively, dysphagia, numbness of the right side of the body, palsy of the left sixth and fourth cranial nerves, miosis, hypalgesia of the right side of the face, blindness, and weakness of the left side of the face, right arm, and both legs. A clinical diagnosis of occlusion of the basilar artery could be made; necropsy was not permitted.

Only one transient episode of vertigo, quadriparesis, diplopia, dysarthria, numbness, and faintness was experienced by this patient. Though no necropsy was performed, the final illness was highly suggestive of occlusion of the basilar artery. The symptoms and findings present on that one occasion fit a pattern easily explainable on the basis of altered function of tissue supplied through the basilar artery.

Thrombosis Within the Basilar Arterial System

When neurologic abnormalities persist, actual damage to the brain can be presumed to have occurred. With careful attention to previous symptomatology, mode of onset, and evaluation of the neurologic examination, the lesion can usually be accurately placed. The importance of this is not theoretical or pedantic but practical, since placing the lesion accurately aids in determination of the cause and in a planned approach to treatment. Although it is recognized that an actual occluded vessel may not be found at necropsy, we have chosen, for the sake of simplicity at this time, to refer to these as instances of thrombosis.

It is characteristic of a high percentage of patients who subsequently die of basilar thrombosis that they have had not only previous transient attacks but also a so-called stuttering onset. In the total course of this condition, the early phase of episodic symptoms would be the syndrome of intermittent insufficiency of the basilar arterial system. Later, a series of neurologic abnormalities appears, often in stepwise fashion, and persists. From this point on, actual infarction, presumably due to thrombosis, may be assumed to be present. If progression of the thrombotic process occurs, the condition of the patient gradually deteriorates. Marked fluctuation from day to day in the various signs, as well as in the whole complex, may be seen. When the basilar artery is occluded, severe neurologic deficits are almost always present and the outlook is grave.

The neurologic signs noted when thrombosis of the basilar artery is in the process of occurring or has actually occurred include the following ones: weakness of the limbs, present as hemiparesis or quadriparesis, although later quadriparesis is usually evident, often with extensor spasms; pseudobulbar or bulbar weakness in the form of dysarthria and dysphagia with a weakened pharynx and palate and slowness and decreased protrusion of the tongue; ocular abnormalities, particularly in the pupils, where inequality, miosis, and nonreaction may be seen, or in the extraocular muscles, which are weakened in various combinations, and homonymous hemianopsia, which may be bilateral, and facial weakness, either "central" or "peripheral" in type. The last, with contralateral hemiparesis, usually indicates involvement of the brain stem. Hyperpyrexia is common.

* Information supplied by Dr. George Ehni, Houston, Texas.

The many brain-stem syndromes are actually fragments of the whole and represent thrombotic processes within the system. In some cases these small focal infarcts apparently occur with little or no tendency for additional cerebrovascular episodes. Many of these may be, however, preludes to involvement of the basilar artery itself. Since no data are available concerning the statistical chance of further trouble, one must be governed by careful observation of the course of the illness. For instance, the appearance of homonymous hemianopsia from occlusive disease, within either the carotid (middle cerebral) or the basilar (posterior cerebral) systems, may be an isolated phenomenon not necessarily implying the likelihood of additional abnormalities in the future. Yet, if a third-nerve palsy should follow closely, evidence is at hand to implicate the region of the basilar crotch and to infer that the pathologic process (thrombosis?) is extending. It cannot be overemphasized that the details of the symptoms and signs and their mode of appearance are extremely important. Some appropriate treatment may be available theoretically to preclude the closure of the main channel, with its devastating consequences. The interruption of this stepwise progression, so characteristic of the thrombotic processes within this system, is the logical goal.

Illustrative Cases

CASE 3.—A 65-year-old man who came to the Mayo Clinic on Dec. 7, 1948, was immediately admitted to the hospital because of weakness and high blood pressure. Several weeks before, he had suffered from headache for a few days, during which period he had several episodes of vertigo, nausea, and vomiting that lasted some 10 to 15 minutes. One week before admission he felt nauseated and vomited; his legs were so weak he could not walk, and his speech was thick. It was said that he protruded his tongue poorly.

On the day of admission he noted weakness again in his legs. Examination revealed a blood pressure of 180 mm. of mercury systolic and 110, diastolic. He could not swallow; the right pupil was larger than its fellow; the legs were weakened moderately; the tongue was protruded weakly and to the left; the muscle-stretch reflexes were more brisk on the left, and the left plantar reflex was extensor in type.

Three days later, after slight improvement in his condition, paralysis of the right limbs and of the left side of the face (peripheral type) occurred. The left external rectus muscle was paralyzed, and the patient was unable to deviate the eyes conjugately to the left. He could not speak, although he appeared to understand. He could not swallow; the palate hung motionless, and there was no pharyngeal reflex. Later in the day the left limbs, as well as the right side of the face, were noted to be gravely weakened. Babinski's reflex was present bilaterally. The right pupil was again larger. The superficial and deep sensations were decreased on the right side. The next day he became comatose, and his temperature began to rise; he died Jan. 11. Necropsy revealed thrombosis of the basilar artery, with infarction of the pons (particularly the left side) and cerebellum.

In this case, vertigo, vomiting, weakness of the legs, and dysarthria were seen as evidence suggestive of insufficiency of the basilar artery. Then the pattern changed and a series of permanent abnormalities appeared. Mild paraparesis, unequal pupils, and dysphagia were seen first. Next, a brain-stem syndrome was noted with a nuclear or peripheral lesion of the facial nerve on the left and contralateral hemiplegia, associated with palsy of the left sixth nerve and ocular deviation to the right (Millard-Gubler-Foville syndrome). More weakness was apparent in the muscles of the oropharyngeal cavity. Soon weakening of the left limbs, coma, and hyperpyrexia occurred.

CASE 4.—During the week preceding admission a 74-year-old man had about a half dozen transient episodes of vertigo and nausea that lasted some 15 minutes. He was admitted on April 9, 1953, because on the previous day he experienced poor vision in the right half of his visual field, ataxic gait, thick speech and dysphagia after an episode of vertigo, nausea, and vomiting. Examination revealed a smaller right pupil, ptosis of the right lid, coarse nystagmus on lateral gazes, right facial weakness, ataxia, right homonymous hemianopsia, and dysarthria and dysphagia. Four days later, after little change in his condition, he lapsed into coma and had spontaneous decerebrate extensor spasms; the tendon reflexes were brisk, and the plantar reflexes were extensor in type; the pupils became miotic and nonreactive. He died the next

day. Necropsy revealed thrombosis of the basilar artery and the left posterior cerebral artery, with infarction of the pons, midbrain, left cerebellar hemisphere, and the calcarine area of the left occipital lobe.

The differential diagnosis of thrombosis within the basilar arterial system might involve many things. Comment concerning expanding masses and convulsive phenomena has been made before. A helpful aid is that hearing is usually not greatly, if at all, affected in basilar occlusion, provided testing is possible. In extramedullary lesions of the posterior fossa, hearing is involved frequently.

When there is bilateral occlusion of the internal carotid arteries, either simultaneously or separately, the differentiation may not be possible. One internal carotid may become occluded without symptoms; later, when its fellow is also occluded, coma with bilateral signs may be seen.

The Syndrome of Intermittent Insufficiency of the Carotid Arterial System

The internal carotid artery and its branches supply blood to the homolateral retina, to the frontal and parietal lobes, and to portions of the temporal lobe, internal capsule, and basal ganglia.

The syndrome of intermittent insufficiency of the internal carotid arterial system [10] consists of attacks of unilateral impairment of motor or sensory function or both. With involvement of the artery to the dominant hemisphere, aphasic disorders may be seen. Decrease in vision or blindness in only one eye (amaurosis fugax), and that on the side of the involved artery, will be seen in some instances. Convulsive activity or alteration in consciousness is deliberately not included in this definition. While the degree of involvement will vary, the complexity is not as great as in vertebral-basilar insufficiency.

Here, too, a single attack may in no way be diagnostic. But a group of attacks consisting of carefully described abnormalities may permit one to make the diagnosis. The patient is symptomless between attacks. If he is examined during an attack, appropriate abnormalities will be noted. The pressure in the central retinal artery on the side of the arterial insufficiency may be decreased continuously.

In 1951, Johnson and Walker [11] tabulated 107 cases of occlusion of the internal carotid artery as determined by cerebral angiography. In some 40% of these cases, previous or premonitory symptoms had been present. However, no emphasis was placed on the use of these symptoms as diagnostic aids or as the precursors to possible thrombosis of the internal carotid artery.

Illustrative Cases

CASE 5.—A 54-year-old man came to the clinic on May 18, 1955, because of weakness in the left limbs. He had suffered from diabetes mellitus, arteriosclerosis obliterans in the lower limbs, and mild hypertension for many years.

Three weeks before admission he had a five-minute episode of blindness in the right eye. In the subsequent weeks prior to admission he had six more similar attacks. He was certain the visual abnormality involved only his right eye, for when he closed this one he could see well with his left. On closing only the left he could not see at all. During these weeks also he had episodes of numbness and poor use of the left upper extremity unrelated in time to the blindness. These would begin with tingling of the skin over the left shoulder, and this would extend down the limb to the fingers. Then he would become aware that the fingers would not perform properly and were weak. The whole episode would last 5 or 10 minutes.

On the day before admission he awakened to find his left limbs weak. Examination disclosed mild paresis of the left arm, particularly in the hand, and minimal weakness in the leg. Finger wiggle and toe tap on the left were decreased. The muscle-stretch reflexes were brisker on the left, and the left plantar reflex was extensor in type. The carotid pulsations and pressures in the central retinal arteries were judged to be within normal limits. The neurologic examination otherwise revealed normal findings.

About a dozen attacks preceded the occurrence of this man's stroke. The transient episodes themselves, constituting the syndrome of intermittent insufficiency of the carotid arterial system, were not associated

with any apparent permanent damage, but the stroke was. The attacks and the stroke involved the area supplied by the right internal carotid artery, suggesting that they all were related.

CASE 6.—A 55-year-old man came to the clinic in April, 1955, because of right hemiparesis and aphasia. In April, 1954, he had the gradual onset of numbness and weakness of the right upper limb and bifrontal headache, the episode lasting some four hours. In November he was hospitalized elsewhere for a suspected myocardial infarction and received bishydroxycoumarin (Dicumarol) for three weeks. On Dec. 17, he noted that his right upper limb was numb, and this persisted. On Dec. 19, weakness developed in the right limbs, and on the next day he had difficulty finding the proper word and spoke in a jargon. When he was examined in January, 1955, mild right-sided spastic hemiparesis and motor aphasia were noted. At that time also, the physician noted decreased pulsations in the left internal carotid artery. The patient's condition improved during the subsequent weeks until he was almost normal.

Several days prior to admission he had a relatively sudden onset of right hemiplegia and difficulty with speech. Examination disclosed a paralyzed right upper limb and a weakened spastic right lower limb and severe expressive aphasia. No pulsations of the left internal carotid artery in the neck or pharynx could be detected. The pulse in the left superficial temporal artery was feeble. Ophthalmodynamometer readings were O. D. 40 mm. and O. S. 10 mm. The electroencephalogram at this time showed evidence of acute destruction in the left temporoparietal area.

Three times this patient suffered from altered function of the left side of his brain. The first was of short duration and left no apparent damage. The second was associated with damage to the left cerebral hemisphere but from which some functional recovery was taking place when the third ictus occurred and massive damage resulted. During several subsequent weeks of observation, little or no return of function was seen. The findings on clinical examination indicating occlusion of the left internal carotid artery imply that insufficiency and later absence of blood flow through this artery were responsible for his symptoms.

The diagnosis of carotid insufficiency can only be suspected in many instances. In some it probably cannot be made early. In others the diagnosis may be established with reasonable certainty, particularly if unilateral blindness and contralateral weakness are present.

The differential diagnosis includes, among other things, convulsive disorders in their various manifestations. Particularly, convulsive phenomena associated with an expanding intracranial mass lesion (as neoplasm, abscess, or hematoma) can mimic this syndrome. The absence of the signs and symptoms of increased intracranial pressure, tonic or clonic activity, altered consciousness, and roentgenographic abnormalities tend to exclude such lesions.

Roentgenograms of the skull should be normal in the insufficiency syndrome. Calcification of the internal carotid arteries in the region of the sella may be noted. Since such calcification may be seen in patients who have no neurologic symptoms, its use for diagnosis is limited. When there is severe atrophy of one of the cerebral hemispheres associated with occlusion of the internal carotid artery, the pineal gland may be shifted to that side. Although we have not yet observed this in the insufficiency syndrome, it is possible that it may occur here also in some instances.

The electroencephalogram should present normal findings between episodes, but after thrombosis with infarction has occurred it may show evidence of destruction (Case 6).

Unilateral decrease in vision, decrease in the retinal arterial blood pressure on the side of the arterial involvement, and decreased pulsation of the common or internal carotid artery in the neck or inside the pharynx (after the manner of Dunning), as well as the nature of the episodes, favor a diagnosis of this syndrome. Forceful palpation or compression of the carotid artery should be avoided because of the possibility of increasing cerebral ischemia.

At times it may be difficult to distinguish between insufficiency of the internal carotid and of the vertebral-basilar arterial systems. When in the latter the episodes

consist of only unilateral impairment of motor or sensory function and other ancillary symptoms are wanting, definite differentiation cannot be made. Decrease in pulsation of the carotid artery or in the central retinal arterial pressure (ophthalmodynamometer) or the presence of aphasic components (when the dominant side is involved) aids in diagnosis. When diplopia, bilateral homonymous hemianopsia, confusion, dysphagia, severe vertigo, and quadriparesis occur, the symptoms probably are consequent to ischemia in the field of the basilar artery.

Consideration must be given to such special studies as pneumoencephalography and arteriography. The former will no doubt have to be performed in some instances to be certain of the absence of an expanding mass lesion. On the other hand, arteriography carries certain hazards in the presence of cerebrovascular disease, and we believe that it should be restricted in use.

Comment

The detailing of these symptom-complexes may seem artificial at first; yet their value appears established. It is our impression that the insufficiency syndromes are commoner than generally believed and can be diagnosed in many instances. Particularly is this true in regard to the vertebral-basilar artery, which, for some reason, has been much neglected heretofore. The diagnosis of intermittent cerebrovascular insufficiency should be made with caution. This is important, for further investigation and observation might yield other etiologic bases for the symptoms. When additional evidence is at hand to establish one of these diagnoses, the physician can institute treatment immediately and with confidence as to the diagnosis.

In instances of the intermittent syndromes—both of the carotid arterial system and of the vertebral-basilar arterial system—the proof of their existence is implied from studies of patients who subsequently die of occlusion of these arteries. Data concerning these have been published elsewhere.[4,10]

It is probable that there are episodic symptoms from involvement of the various individual branches of these major vessels. We have chosen the broader connotation, since the other would seem to be too fine a distinction. Moreover, it is our feeling that too much attention has been directed in the past to the individual branches, thus excluding from consideration the main vascular channels themselves. This is logical, since narrowing of the proximal channel necessarily influences the blood flow of all of the more peripheral branches to various degrees at various times. Little attention has been paid to these vessels at necropsy, and this may well be one factor to account for the presumed high incidence of infarction without demonstration of an actual occluded vessel.

The course of the syndromes of intermittent insufficiency varies and may last for years. The frequency, however, tends to increase in those in whom thrombosis finally occurs.

Summary

Some antecedent phenomena and their use in the anticipation and early recognition of certain types of strokes are discussed, and an outline of the course of events that may lead up to occlusion of certain major vessels to the brain is presented. Three syndromes are delineated: the syndrome of intermittent insufficiency of the vertebral-basilar arterial system, the syndrome of thrombosis within the basilar arterial system, and the syndrome of intermittent insufficiency of the internal carotid arterial system. The concept of anticipation embodies the use of these antecedent phenomena to suspect the possibility of future thrombosis with resultant damage to the brain. Early recognition, early treatment, and prevention are involved in this concept. With early recognition of these types of cerebrovascular disease, treatment may be instituted prior to the possible occurrence

of extensive cerebral infarction. It appears that treatment with anticoagulant drugs may prevent the continuation of these ischemic attacks and therefore also the possible occurrence of a catastrophic infarction.

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A Twenty-Year Appraisal of BCG Vaccination in the Control of Tuberculosis

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Few topics in the field of tuberculosis have engendered such divergent opinions as has the use of BCG vaccination in the control of tuberculosis. The views held by the medical profession in the United States on this subject have been either adversely critical, enthusiastic, or skeptical. Unfortunately, some of the unfavorable views have been expressed by those who have had no first-hand experience in this field and whose opinions have been often based on selected reports rather than on a critical review of the available literature. On the other hand, there was little justification for the enthusiasm of some advocates, based as it was on the results either of uncontrolled studies or of studies which were open to criticism.

Although the introduction of antimicrobial agents ushered in a new era in the treatment of tuberculosis, the prophylactic value of these agents for man remains to be proved. Foci of tuberculous infection persist in certain areas and among certain groups, despite the marked reduction among the general population in the morbidity and mortality from the disease. This situation emphasizes the importance of using an immunizing agent in order to protect those who have escaped tuberculous infection but who may be exposed later to this disease.

It is pertinent to point out that public health agencies and the medical profession in general have long accepted immunizing agents for self-limited diseases with a morbidity and mortality significantly lower than that of tuberculosis. The English lay journal *The Economist*[1] contrasts the eagerness of the British Ministry of Health in recommending the use of poliomyelitis vaccination with its reluctance to accept vaccination in the control of tuberculosis. This, despite the fact that in 1954, during the greatest epidemic year of poliomyelitis in England and Wales, there were 7776 cases of poliomyelitis with 700 deaths in contrast to 335,000 cases of tuberculosis and about 8000 deaths.

The long history of many investigations to increase resistance to tuberculosis includes the use of chemical fractions and metabolic products of the tubercle bacillus, of tubercle baccilli killed by chemical or physical agents, and of viable related mycobacteria. Thus far, none of these agents have significantly increased resistance of susceptible animals to infection against virulent tubercle bacilli. On the other hand, increased resistance to tuberculous infection has been observed repeatedly by different investigators after the use of minute numbers of viable virulent tubercle bacilli or of large numbers of viable organisms from attenuated strains of tubercle bacilli. The fact that viable virulent tubercle bacilli may multiply in situ and generalize makes it dangerous to use such a vaccine for man. On the other hand, vaccine prepared from certain viable attenuated strains of tubercle bacilli is safe for man, since it induces a primary tubercle in situ and tends to remain localized or to be limited to the regional lymph nodes.

The importance of viability in an immunizing agent has been shown by Smithburn and Lavin.[2] They found that virulent tubercle bacilli, exposed to ultraviolet light to the point where they were attenuated but

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viable, increased the resistance of guinea pigs to tuberculous reinfection. On the other hand, the same virulent culture when killed by ultraviolet light failed to increase resistance.

Increased resistance following a primary tuberculous infection is indicated by the infrequency of a secondary primary complex, the containment and disappearance of viable tubercle bacilli in arrested lesions, the chronicity of the lesions of reinfection, and especially the infrequency of bacillemia and hematogenous spread of the disease to other organs.

The precise studies of Willis [3,4] and of Krause [5] on the mechanism of tuberculoimmunity, with use of guinea pigs previously treated with the viable attenuated R 1 tubercle bacillus, showed not only that the migration of the virulent H 37 tubercle bacillus from the site of infection was greatly retarded but that the rate of development of the tuberculous process was decreased, the extent was less marked, and the lesions soon became chronic in character.

The studies of Calmette and Guérin,[6] using a viable attenuated bovine type tubercle bacillus designated BCG, "Bacille Calmette-Guérin," indicated that animals treated with the culture developed increased resistance to a challenge dose of viable virulent tubercle bacilli. This BCG culture was derived from an originally virulent bovine strain and was attenuated by repeated passage over a period of 13 years on beef-bile-containing medium. The attenuated culture retained all of its original characteristics, except that it was no longer capable of inducing progressive tuberculosis in animals as susceptible as the guinea pig. The logic, therefore, for using vaccine prepared from viable attenuated strains of tubercle bacilli, such as BCG, vole, or R1RA, in those who have escaped tuberculous infection is evident. Such vaccines are capable of producing a localized, self-limited, primary tubercle resulting in increased resistance to tuberculous infection. Vaccination is not indicated for persons with a positive tuberculin reaction, since such a reaction reflects a previous tuberculous infection, followed by increased resistance.

BCG vaccine was first administered per os to newborn infants in 1921. Since then it has been administered to more than 100,000,000 persons of all ages, many living under the most adverse hygienic, social, and economic conditions. The safety of the vaccine for man is attested by the fact that, despite its widespread use, of the cases of tuberculosis reported as being due to BCG vaccine, only four atypical cases of tuberculosis nonresponsive to antimicrobial agents seem to have resulted from BCG vaccination. No reports have been made thus far of any multiple cases of tuberculosis attributable to vaccine from one laboratory or to any one lot or one vial of BCG vaccine. This record compares most favorably with that of other immunizing agents which have been administered to man.

The determination of the value of BCG vaccine, as of any immunizing agent, requires first that it be developed and tested in the laboratory in susceptible animals under strict control conditions. The final proof, however, of the efficacy of such agents must be found in the results of field studies, conducted under control conditions and in areas where the disease occurs in significant numbers and where observations can be made over a significant period of time.

Although proof of the safety of BCG vaccine has been demonstrated, its specific protective value for man has not been as firmly established. This has been due to the fact that, with but few exceptions, studies have not been conducted under control conditions over a sufficiently long period of time and to the difficulty of assessing the results of vaccination over a period in which there has been an almost universal continuing decrease in morbidity and mortality from tuberculosis even antedating the use of BCG vaccine and antimicrobial agents.

In an attempt to appraise, under field conditions, the specific protective value of

BCG vaccine in the control of tuberculosis, a joint investigation was undertaken by the Henry Phipps Institute, the University of Pennsylvania, and the Branch of Health, Bureau of Indian Affairs, Department of the Interior, now the Division of Indian Health, Department of Health, Education, and Welfare. This study was initiated between December, 1935, and February, 1938.

Following a reconnaissance of many Indian agencies, pueblos, and towns of southeastern Alaska, it was decided to conduct a study on the specific protective value of BCG vaccine under control conditions among eight different Indian tribes living in five widely separated geographical areas. They were the Pima tribe, Pima Agency, Arizona; the Shoshone and the Arapaho tribes on the Wind River Agency, Wyoming; the Chippewa tribe on the Turtle Mountain Agency, North Dakota; the Sioux tribe of the Rosebud Agency, South Dakota, and the Thlingit, Haida, and Tsimshian tribes, living in 12 communities of southeastern Alaska. These widely scattered groups were selected since they represented non-nomadic tribes whose mode of living made it possible to follow them over a long period of time. Economic, social, and dietary patterns were fairly uniform for all those living on the same agency. At the beginning of the study and until the post-World War II period economic conditions in all areas were uniformly low, housing was poor and crowded, and morbidity and mortality from tuberculosis were reported as being high. In recent years economic conditions have improved in some areas but overcrowding continues. Climatic conditions varied in the different geographical areas, as did cultural patterns, racial stock, and dietary habits of the people.

Plan of Study

In the absence of precise information on the mortality and morbidity from tuberculosis as well as on the incidence of tuberculous infection among the Indian tribes included in the study, it was decided first to determine the incidence of tuberculous infection by means of the intracutaneous tuberculin test.

Between December, 1935, and January, 1938, an initial tuberculin test was given to a total of 8420 Indians ranging in age from less than 1 year to 60 years and over. This group represented an unselected cross section of the general population and included all children attending government and denominational schools on the 4 Agencies and in the 12 communities of southeastern Alaska.

The initial intracutaneous injection of 0.00002 mg. of trichloracetic acid purified protein derivative tuberculin (PPD) was made in the forearm. Readings were made 48 hours after the injection, and if the reaction was negative or doubtful a second injection of 0.005 mg. of the same tuberculin was given and readings again made 48 hours later. The same preparation of purified protein derivative tuberculin, supplied by Dr. Florence Seibert, of the Henry Phipps Institute, was used for the first five years of the study. After that time an ammonium sulfate purified protein derivative tuberculin (PPD-S), also supplied by Dr. Seibert, was used in the same amounts. The dilutions of the purified protein derivative tuberculin were prepared daily from the concentrated solution and were not used when more than 24 hours old. The injections and the interpretation of the tuberculin reactions were, with but few exceptions, made by the same persons throughout the study.

The results of this base-line study[7] indicated that the incidence of tuberculous infection, in five-year age periods, varied but little on the different agencies. Hypersensitivity to tuberculin is marked among American Indians, as it is among others who have received repeated exposures to viable virulent tubercle bacilli. Of those who originally reacted to the initial injection of 0.00002 mg. of PPD tuberculin, approximately 5% had a 4+ reaction characterized by vesiculation or necrosis. The per cent of those who reacted to 0.00002 mg. PPD

tuberculin increased rapidly in successive five-year periods. Thus, of those under 5 years of age, 12.7% reacted, while among the 20- to 24-year group 90.0% reacted.

After the completion of the initial tuberculin testing on each agency, cards were prepared for all those under 20 years of age who had failed to react to both 0.00002 and 0.005 mg. of PPD tuberculin. These cards were first sorted by school or school district, then by year of birth and sex. The cards arranged by sex and year of birth were then divided by alternation into two groups. One group received an intracutaneous injection of either 0.1 or 0.15 mg. of freshly prepared BCG vaccine in the skin over the region of the deltoid muscle. The other group received an intracutaneous injection of 0.1 ml. of isotonic sodium chloride solution at the same site and served as controls. The site of injection in both groups was examined 48 hours later to note whether or not a local exaggerated inflammatory reaction (Koch phenomenon) had occurred. In a small number of instances a person originally designated to receive vaccine was absent from school and a person originally designated as a control was substituted. A total of 1551 males and females ranging in age from less than 1 year to 19 years received BCG vaccine, and 1457 males and females of comparable age received isotonic salt solution and served as controls. Neither the vaccinated nor the controls were isolated before or after their inclusion in this study, nor was their mode of living modified because of the study. None of the vaccinated were revaccinated. Of the 3005 persons included in this program, approximately 85% were examined roentgenologically shortly after they received their initial tuberculin test.

Reexaminations

Tuberculin tests and roentgenological examinations of the chest were carried out annually on all agencies through 1944 and again in 1947, on both vaccinated and controls, covering 9 to 11 years of observation. The per cent of BCG-vaccinated who were tuberculin-tested annually ranged from 96.4% one year after the initiation of the study to 68.6% in the war year 1944. Among the controls the per cent tuberculin tested ranged from 95.4% to 70.4%. Among the vaccinated the per cent who were examined roentgenologically ranged from 97.4% to 69.9% and among the controls, from 96.8% to 72.1%.

The same procedure was used in the annual tuberculin testing as for the initial test. At the time of each annual tuberculin testing x-ray examinations of the chest were made.

Aronson, Parr, and Saylor[8] found that the sensitivity to tuberculin following BCG vaccination is usually less marked than that following infection with virulent tubercle bacilli. During the first 11 years of the annual tuberculin testing the per cent of the vaccinated who reacted to both 0.00002 and 0.005 mg. of PPD tuberculin ranged from 87.5% to 94.9%. Among the vaccinated, as among the controls, natural infection with virulent tubercle bacilli must have occurred. This is indicated by the fact that the per cent who reacted to 0.00002 mg. of PPD tuberculin rose from 36.7% one year after vaccination to 61.4% after eleven years. Among the controls 12.7% reacted to both doses of tuberculin 1 year after the initial negative reaction, and the annual increment of positive reactions for the first 11 years was approximately 5%, reaching 41.7% after 11 years. The tuberculin sensitivity among the controls was high, as indicated by the fact that of the 41.7% who reacted at the end of 11 years 35.5% were positive to 0.00002 mg. and only 6.2% to 0.005 mg. of PPD tuberculin.

Between 1936 and 1947 a total of 13,660 roentgenograms of the chest were taken of 1541 BCG-vaccinated persons and 12,920 of 1451 controls, an average of 8.86 and 8.9 roentgenograms for the vaccinated and controls, respectively. The large 14×17 in. x-ray films were used for all persons except infants. These films were originally read by a roentgenologist attached to the BCG field unit. At the end of six years a review of

all films to that date was made by Dr. H. B. Zwerling, radiologist of the Tuberculosis Control Division, U. S. Public Health Service. At the conclusion of the annual examinations after 9 to 11 years of the study and in order to have the interpretations of the films as uniform as possible all x-rays were interpreted by a roentgenologist with extensive experience in interpreting x-rays of the chest. This roentgenologist had not been associated with the study previously and had no knowledge of the tuberculin reaction or whether the films represented those of a BCG-vaccinated or a control person. The roentgenograms were interpreted alphabetically and serially by agency or community. Stein and Aronson [9] reported that abnormal pulmonary shadows from all causes were observed in 16.7% of the films of the BCG-vaccinated and in 31.2% of the films of the controls. Lesions having the roentgenological characteristics of pulmonary tuberculosis were found in 4.1% of the vaccinated and in 16.4% of the controls. Nontuberculous pulmonary lesions were found in 12.5% of the vaccinated and in 14.8% of the controls. Of special significance is the fact that among the vaccinated no x-ray evidence of miliary tuberculosis was found in any case, while among the controls 10 persons, or 0.7%, showed such lesions.

Statistical analysis of the x-ray findings indicate that the cumulative annual attack rate from tuberculosis at the end of the 9- to 11-year period of the field study was 3.52 for the vaccinated and 17.19 for the controls who were at risk. The annual attack rate from nontuberculous pulmonary lesions at the end of the same period was 10.02 for the vaccinated and 14.62 for the controls.

With an increasing appreciation of the geographic distribution of pulmonary lesions which simulate tuberculosis roentgenographically and with a realization that the diagnosis of pulmonary tuberculosis based solely on the interpretation of roentgenograms is subject to significant error even in the hands of well-qualified radiologists,[10] additional means must be considered for identifying the specific nature of pulmonary lesions. For this purpose intracutaneous tests with certain specific antigens, such as tuberculin, histoplasmin, and coccidioidin, are of value. Since Aronson, Saylor, and Parr [11] demonstrated a high incidence of coccidioidin sensitivity among the Pima Indians of Arizona, in association with a high incidence of calcified pulmonary lesions in tuberculin-negative persons, a study of the relation of the tuberculin reaction with the occurrence of pulmonary lesions was indicated.

After the interpretation of the x-ray films by Stein and Aronson,[9] Aronson and Aronson [12] correlated the results of the tuberculin test with the x-ray interpretation. Among the controls the tuberculin reaction converted from negative to positive with 0.00002 mg. of PPD tuberculin in from 70% to 85% of cases diagnosed as primary, minimal, or moderately advanced tuberculosis or pleural effusion. Of the persons who developed miliary tuberculosis, 50% gave a positive reaction. On the other hand, the tuberculin reaction of those showing nontuberculous lesions and of those with no pulmonary lesions converted from negative to positive in 37% and in 27.8%, respectively.

The correlation of pulmonary lesions with tuberculin hypersensitivity in BCG-vaccinated persons is complicated by the fact that a positive tuberculin reaction may be the result of either BCG vaccination, a superimposed tuberculous infection, or both. However, since hypersensitivity following BCG vaccination is usually of a low level, a definite increase in sensitivity may be interpreted as being due to a superimposed tuberculous infection. Although the small number of cases of tuberculosis among the vaccinated does not permit drawing statistically significant conclusions, it is noteworthy that among the 40 cases of primary tuberculosis which developed in this group 75% reacted to the first dose of 0.00002 mg. of PPD tuberculin.

The annual tuberculin tests for the first 9 to 11 years of this study offered an opportunity to correlate the tuberculin test with fatal tuberculosis. The results of this phase of the study have been reported previously.[13] In summary, it was found that among the controls only 8 of the 31 fatal cases of generalized tuberculosis had reacted to tuberculin previous to the year of death, while of the 32 controls who died from pulmonary tuberculosis 29 had reacted to tuberculin either before or during the year of their death. Of the 12 BCG-vaccinated who died from tuberculosis during the first 11 years of the study, all showed a high level of tuberculin hypersensitivity, except one who had died 3 months after vaccination and although originally tuberculin-negative had shown a marked Koch phenomenon 48 hours after vaccination.

With the completion of the reexaminations of both groups in 1947 it was decided to discontinue the annual examinations but to follow both groups at approximately five-year intervals in order to determine the mortality from all causes and from tuberculosis. The morbidity and mortality from tuberculosis and the mortality from all causes in both BCG-vaccinated and controls have been compared and the results published after 3, 6, and 11 years of observation,[7,14,15] as have the mortality rates from all causes and from tuberculosis for the period 13 to 15 years after the initiation of the study.[13]

Present Study

In order to appraise further the protective value of BCG vaccine, an 18- to 20-year follow-up was conducted in 1956 and was confined to determining mortality from all causes and from tuberculosis. All areas originally included in this study were visited, and through the cooperation of the administrative staffs of the different agencies, the Arizona Health Department, and the Alaska Territorial Health Department and through direct contact with many of those in the study and with their contemporaries, it was possible to trace the whereabouts of 1547, or 99.7%, of the original 1551 who received BCG vaccine and of 1448, or 99.4%, of the original 1457 who served as controls. Reported deaths were checked in each area against death certificates at the hospital or agency office as well as against probate records dealing with the estate of the deceased and with the reports of the local public health nurse.

TABLE 1.—*Diagnostic Criteria for Deaths from Tuberculosis in BCG-Vaccinated Persons and Controls*

Diagnostic Criteria	Clinical Diagnosis									
	Pulmonary Tuberculosis		Tuberculosis Meningitis		Military Tuberculosis		Tuberculosis Bone & Joint		Tuberculosis Peritonitis	
	BCG, No.	Control, No.	BCG, No.	Control, No.	BCG, No.	Control, No.	BCG, No.	Control, No.	BCG, No.	Control, No.
X-ray pos., acid-fast bacilli pos.	3	18	1	1	0	5	1	1	0	0
X-ray pos., acid-fast bacilli neg.	2	2	0	0	0	0	1	1	0	1
X-ray pos., no laboratory studies	2	19	0	0	0	7	0	1	0	1
X-ray pos., autopsy pos.	0	0	2	1	0	0	0	0	0	1
X-ray pos., clinically pos.	0	0	0	3	0	0	0	0	0	0
X-ray pos., pleocytosis, spinal fluid	0	0	0	2	0	0	0	0	0	0
X-ray neg., acid-fast bacilli pos.	0	0	0	1	0	0	0	0	0	1
X-ray neg., pleocytosis, spinal fluid	0	0	0	2	0	0	0	0	0	0
No x-ray exam., autopsy pos.	0	0	0	0	1	0	0	0	0	0
Total	7	39	3	10	1	12	2	3	0	4

The cause of death as stated in the death certificate was not accepted per se, but substantiating evidence to support the diagnosis was required from clinical records, laboratory findings, and from data obtained from household members of the deceased.

The criteria used to establish a diagnosis of tuberculosis in both vaccinated and controls are presented in Table 1.

It will be noted from this Table that the diagnosis of tuberculosis was established in all but four controls and one vaccinated by x-rays of the chest, supported in a high per cent of cases by the finding of acid-fast bacilli in the sputum or spinal fluid or by pleocytosis of the spinal fluid. The fatal case of miliary tuberculosis occurred 16 years after vaccination in a person who was not examined roentgenologically during the course of her last illness. The diagnosis was established by autopsy and histological findings.

It is evident from Table 1 that with but few exceptions the acute hematogenous forms of tuberculosis occurred among the controls. The 13 deaths from tuberculosis among the vaccinated include two who had shown a definite Koch phenomenon 48 hours after vaccination, thus indicating a tuberculous infection prior to vaccination. One of these died three months after vaccination from tuberculous meningitis, and the other, nine years later from pulmonary and meningeal tuberculosis. Another death was that of a child who had received vaccine of low potency and who failed to react to tuberculin one year later. In another instance death was due to a postoperative hemorrhage 24 hours after a pulmonary resection.

The effectiveness of BCG vaccine is best evaluated by a comparison of mortality from tuberculosis among the vaccinated and controls. Such an evaluation would be more conclusive if the record of every death included the results of laboratory and x-ray examination and autopsy findings. In the absence of such supporting data for every fatal case, a comparison of deaths from all causes during the 18 to 20 years of this study shows that among the vaccinated a total of 104, or 6.7%, of the 1547 persons traced in 1956 had died, while 150 deaths, or 10.4%, had occurred among the 1448 controls, a ratio of 1:1.5. The comparability of the vaccinated and controls is underscored by the fact that deaths from nontuberculous disease occurred in 3.0% of the vaccinated and in 2.9% of controls, while deaths from violence, such as automobile accidents, drowning, or war casualties, occurred in 2.9% each of vaccinated and of controls. On the other hand, the number and per cent of deaths from tuberculosis among the two groups showed a striking difference. By 1956 a total of 13, or 0.84%, of the vaccinated had died of tuberculosis, as compared with 68, or 4.7% of the controls, a ratio of 1:5.2. Among the vaccinated tuberculosis was responsible for 12.5% of all deaths, while among the controls tuberculosis was responsible for 45.3% of all deaths.

During the quinquennium 1951-1956, there were 32 deaths from all causes among the vaccinated and 22 deaths among the controls. Among the vaccinated, 1 of these was due to tuberculosis confirmed by autopsy; 7, to nontuberculous disease, and 24, to violence. Among the controls in this five-year period 3 deaths were due to tuberculosis; 4, to nontuberculous disease, and 15, to violence. Relative to the larger number of deaths from violence among the vaccinated it must be pointed out that since there were 94 more persons in the original vaccinated group than among the controls and since the total number of deaths from 1936 to 1951 was lower among the vaccinated, it is obvious that a larger number of the vaccinated than controls survived and were at risk of dying during 1951-1956.

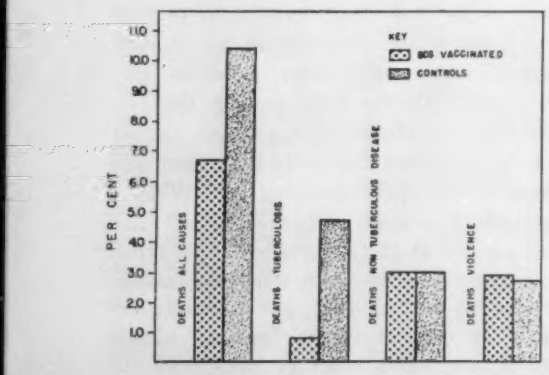
Table 2 summarizes by agency and tribe the number of BCG-vaccinated and controls originally included in the study, the number accounted for in 1956, the total number and per cent of deaths from all causes, from tuberculosis, from nontuberculous disease, and from violence. The Figure represents graphically the per cent of total deaths,

TABLE 2.—*Mortality from All Causes, Tuberculosis, Nontuberculous Diseases, and Violence, by Agency and Tribe from 1936 to 1956*

Agency	Tribe	Time Vaccinated	Group	Original No., 1936–1938	No. Traced, 1956	Cumulative Deaths, All Causes 1936–1956		Cumulative Deaths, Tuberculosis 1936–1956		Cumulative Deaths, Nontuberculous 1936–1956		Cumulative Deaths, Violence 1936–1956	
						No.	%	No.	%	No.	%	No.	%
Pima, Arizona (Series A)	Pima	Feb. 1936	BCG	258	256	20	7.8	2	0.78	7	2.7	11	4.3
			Control	263	261	30	11.5	10	3.8	7	2.7	13	5.0
Wind River, Wyoming	Shoshone	July 1936	BCG	110	110	7	6.4	0	..	4	3.7	3	2.7
			Control	85	85	14	16.5	10	11.7	2	2.4	2	2.4
Wind River, Wyoming	Arapaho	July 1936	BCG	118	118	12	10.2	2	1.7	4	3.4	6	5.1
			Control	106	106	22	20.7	10	9.4	7	6.6	5	4.7
Turtle Mountain, N. D.	Chippewas	Oct. 1936	BCG	170	170	6	3.5	0	..	5	2.9	1	0.6
			Control	162	161	9	5.6	2	1.2	2	1.2	5	3.2
Pima, Arizona (Series B)	Pima	Feb. 1937	BCG	96	96	6	6.2	0	..	4	4.1	2	2.1
			Control	86	86	8	9.3	4	4.6	2	2.3	2	2.3
Rosebud, S. D.	Sioux	Oct. 1937	BCG	301	301	18	6.0	4	1.3	9	3.0	5	1.7
			Control	291	290	17	5.8	9	3.1	5	1.7	3	1.0
Alaska, Southeastern	Thlingit Haida Tsimshian	Jan. 1938	BCG	498	496	35	7.0	5	1.0	13	2.6	17	3.4
			Control	464	459	50	10.9	23	5.0	17	3.7	10	2.2
Total			BCG	1,551	1,547	104	6.7	13	0.84	46	3.0	45	2.9
			Control	1,457	1,448	150	10.4	68	4.7	42	2.9	40	2.9

deaths from tuberculosis, from nontuberculous disease, and from violence among the vaccinated and controls.

This study offered an opportunity to determine differences in mortality from tuberculosis, if any, among Indian tribes of differing racial stock and geographic location. The Shoshone and Arapaho tribes of the Wind River Agency, Wyoming, are of particular interest. These two tribes differ in racial stock and notably in build and physicial appearance. The Shoshones, who are indigenous to this area, have a relatively high admixture of white blood from the time of the early trappers and traders. On the other hand, the Arapahoes, who were assigned to this reservation in 1887 from their original plains habitat, represent a relatively pure Indian stock. The per cent of deaths from tuberculosis among the vaccinated of these two tribes, and, in fact, among the other tribes, is too small to be statistically significant. However, the study of mortality from tuberculosis among the control group of the Shoshone and Arapaho tribes reveals a similarly high rate among both tribes despite differences in their racial stock in the per cent of mixed and full bloods.



Deaths from all causes, tuberculosis, nontuberculous disease, and violence in BCG-vaccinated and controls 1936-1956.

Although there are differences in the per cent of deaths occurring in different climatic areas, these do not seem to justify conclusions as to a relationship between climate and mortality from tuberculosis. There are other variations—in tribe, in the number of foci of infection, and in many other intangible factors which complicate such an evaluation. We do point out, however, that the lowest per cent of deaths from tuberculosis occurred among the Chippewa tribe of the Turtle Mountain Agency, North Dakota, where the winters are long and severe. The per cent of deaths from tuberculosis among the Pima Indians, Arizona,

TABLE 3.—*Cumulative Mortality from Tuberculosis and Nontuberculous Causes in BCG-Vaccinated and Controls 1936-1956 Inclusive*

Observation, Yr.	BCG Vaccination								Control							
	Alive at Start of Year, No.	Untraced After This Year, No.	No. Died This Year			Cumulative Death Rate/10,000			Alive at Start of Year, No.	Untraced After This Year, No.	No. Died This Year			Cumulative Death Rate/10,000		
			Total	TBC	Non-TBC	Total	TBC	Non-TBC			Total	TBC	Non-TBC	Total	TBC	Non-TBC
0-1	1,551		12	1	11	77	6	71	1,457		8	1	7	55	7	48
1-2	1,539		2		2	90	6	84	1,449		14	5	9	151	41	110
2-3	1,537		9	2	7	148	19	129	1,435		8	6	2	206	82	124
3-4	1,528		6	1	5	187	26	161	1,427		8	1	7	261	89	172
4-5	1,522		3		3	206	26	180	1,419		15	9	6	364	151	213
5-6	1,519		1		1	213	26	187	1,404	1	7	4	3	412	178	234
6-7	1,518		4		4	230	26	213	1,396	1	5	3	2	446	198	248
7-8	1,514		7	1	6	284	32	252	1,390		8	5	3	501	232	269
8-9	1,507		7		7	329	32	297	1,382		16	7	9	611	280	331
9-10	1,500		4	1	3	355	39	316	1,366		13	8	5	700	335	365
10-11	1,496		4	2	2	380	51	329	1,353		9	5	4	762	369	393
11-12	1,492		4		4	406	51	355	1,344	1	6	4	2	804	397	407
12-13	1,488		6	3	3	445	71	374	1,337		5	2	3	838	411	427
13-14	1,482	3	6		6	484	71	413	1,332	6	10	4	6	907	439	468
14-15	1,473		4	1	3	510	77	433	1,316		5	2	3	941	453	488
15-16	1,469	2	6	1	5	548	83	465	1,311	1	3	1	2	982	460	502
16-17	1,461		9		9	606	83	523	1,307		1	1	0	989	467	502
17-18	1,452		4		4	632	83	549	1,306		3	0	3	990	467	523
18-19	1,448		4		4	658	83	575	1,303		5	0	5	1,024	467	557
19-20	983		1		1	668	83	585	890		1	0	1	1,034	467	567
20-21	610		1		1	683	83	600	538		0	0	0	1,034	467	567
Total		5	104	13	91					10	150	68	82			

TABLE 4.—*Relationship of Age and Sex to Mortality from Tuberculosis, Nontuberculous Disease, and Violence*

Attained Age at Death, Yr.	BCG-Vaccinated						Controls					
	Tuberculosis		Nontuberculous		Violence		Tuberculosis		Nontuberculous		Violence	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Under 5	0	0	4	7	0	0	2	0	4	6	0	1
5–9	1	0	3	2	2	1	1	4	4	3	3	0
10–14	1	3	4	3	2	0	3	10	2	4	4	2
15–19	1	1	3	7	11	0	12	19	6	5	5	2
20–24	1	3	2	5	11	4	7	9	3	2	14	6
25–29	2	0	2	4	12	0	0	1	0	3	2	0
30–34	0	0	0	0	1	1	0	0	0	0	1	0
Total	6	7	18	28	39	6	25	43	19	23	29	11

in a dry hot desert country, exceeds that noted on the Turtle Mountain Agency and is but slightly lower than the per cent who died from tuberculosis in damp cold southeastern Alaska.

A more precise statistical measure of the differences in the mortality among the vaccinated and controls can be made by determining the cumulative mortality rate from all causes, from tuberculosis, and from nontuberculous causes of those who were at risk of dying for each year during the 20 years of this study. Table 3 lists the number alive each year of the study, the number who died, and the cumulative death rate per 10,000 for the BCG-vaccinated and controls for each year of observation.

The cumulative death rate from all causes was significantly higher each year among the controls than among the vaccinated, with the exception of the first year of the study. At the end of 20 years of observation the cumulative death rate from all causes was 683 for the vaccinated and 1034 for the controls. The cumulative mortality from tuberculosis among the vaccinated rose gradually for the first 10 years, increased sharply during the 10- to 14-year period, then stabilized at 83 per 10,000 for the remainder of the period of observation. On the other hand, among the controls the cumulative mortality rate from tuberculosis rose sharply and rapidly after the first year, reaching a rate of 467 after 16 years of observation, where it remained for the remainder of the study. This would indicate that under the conditions of this investigation the value of BCG vaccine as a specific immunizing agent could have been determined after 15 years of observation, since the increase in the last 5 years has not been marked. The cumulative mortality rates from nontuberculous causes among the vaccinated and controls are almost parallel, rising gradually and steadily with increasing time to a rate of 585 for the vaccinated and 567 for the controls by the end of the study.

Mortality in Relation to Age and Sex

This study offered the unique opportunity of following a preschool- and school-age population which during the period of the study remained generally in the same areas, with no great changes in social and economic conditions.

Table 4 presents the number of deaths from tuberculosis, nontuberculous disease, and violence in BCG-vaccinated and controls in relation to their attained age at the time of death and according to sex.

It will be noted from this Table that the preponderance of deaths from tuberculosis both among BCG-vaccinated females as well as among the unvaccinated males and females of the control group occurred between the ages of 10 and 24. Among the 814 BCG-vaccinated females 7, or 0.85%, and 6, or 0.81%, of the 737 vaccinated males died of tuberculosis. On the other hand, among the 719 female controls 43, or 6.0%, and of the 738 males 25, or 3.3%, died of tuberculosis. The 2:1 ratio of tuberculosis deaths among the females and males of the control group, in contrast to the 1:1 ratio of tuber-

culous deaths among the females and males of the vaccinated group, is additional proof of the specific protective value of BCG vaccine.

The number of deaths from nontuberculous disease showed no significant differences among the vaccinated and controls either by sex or by attained age at death.

A study of the occurrence of deaths from violence shows the expected preponderance of males over females. It will be noted that most of the deaths occurred in the 15- to 29-year period. Of the 39 deaths from violence of vaccinated males, 13 were due to automobile accidents; 6, to war casualties; 8, to drownings; 4, to suicides, and the remaining 8, to other forms of violence. Of the six females who died from violence, one each died from automobile accident, drowning, acute alcoholism, and burns and there were two suicides. Of the 29 male controls who died from violence, death in 9 was due to automobile accidents; in 6, to war casualties; in 4, to drowning, in 4, to accidental gunshot wounds, and in the remaining 6, to other forms of violence. In the 11 female controls, 3 deaths were caused by automobile accidents; 4, by drowning, and the remaining 4, by other forms of violence.

Comment

Although over 100,000,000 persons have received BCG vaccine since 1921, skepticism remains, particularly in the United States, as to its protective value against tuberculosis. The criticism that little is known about the value of BCG vaccine is not substantiated in view of the numerous laboratory studies and controlled field investigations in human populations which have been conducted in the United States, Canada, and the Scandinavian countries.

The determination of the prophylactic value of an immunizing agent such as BCG vaccine should be conducted in areas where a high morbidity and mortality from tuberculosis exists. The number of tuberculin-negative persons which make up the study should be sufficiently large, and the number accounted for at the end of the study should be adequate for statistical analysis. The vaccinated and control groups must be selected at random from the tuberculin-negative persons. The diagnostic criteria should be based on objective diagnostic procedures, such as physical, roentgenological, bacteriological, and pathological examinations, rather than on case reports or death certificates per se. The periods of observation for both vaccinated and control groups should be contemporary. Last and most important is the use of BCG vaccine with high antigenicity at the time of injection, as indicated by conversion of the original tuberculin reaction from negative to positive.

It must be noted here that the studies of Shaw and Palmer [16] do not support the findings of other investigators as to the protective value of BCG vaccine. Although their studies include larger numbers than that of other investigators, the follow-up and diagnostic criteria differed from that used in other control studies. The studies in Muscogee County, Georgia, were conducted in an area so free of tuberculosis that after four years of observation there were no deaths from tuberculosis among either the vaccinated or the controls, while the cases of tuberculosis were 5.2 and 6.5 per 100,000 for the 16,900 vaccinated and 17,200 controls, respectively. The authors conclude that "in a community like Muscogee County, there is not much tuberculosis that can be influenced by BCG or any other immunization procedure."

In the studies conducted in Puerto Rico no deaths from tuberculosis were reported among the 50,200 vaccinated and 27,300 controls who had been followed for four years. The tuberculosis morbidity rate based on existing notification systems was 31.2 per 100,000 for the vaccinated and 46.4 for the controls. Assuming that the diagnostic acumen and criteria used by the attending physicians in reporting the cases were the same, such a procedure fails to take into consideration the number of cases of

primary tuberculosis, which in most instances can be diagnosed only by roentgenological examination. Thus Stein and Aronson [9] found roentgenological evidence of primary tuberculosis in 2.6% and 9.7% of BCG vaccinated and controls, respectively.

Although the studies of Shaw and Palmer involved large number of persons, there is no indication in their report of the antigenicity of the BCG vaccine used in their investigations. While it is fair to assume that there was no bias in diagnosing tuberculosis in favor of one group over the other, without some knowledge of the potency of the vaccine at the time of injection coupled with variations in the diagnostic acumen, criteria, and interest in reporting cases of tuberculosis the results must be considered inconclusive.

The decline in the occurrence of tuberculosis, which antedates the discovery of the tubercle bacillus and which has accelerated in recent years, has made it more difficult to assess the role of immunizing agents and other prophylactic measures in the control of tuberculosis. Aronson and Taylor [17] found that the incidence of reaction to 0.00002 mg. of trichloracetic acid PPD among school children on certain Indian agencies included in the BCG and other field studies had decreased in the 5- to 9-year age group from 31.3% noted in 1936-1938 to 11.7% in 1954. In the same period in the 10- to 14-year age group the per cent of tuberculin reactors decreased from 57.0% to 22.8% and in the 15- to 19-year age group, from 81.0% to 44.6%. These reductions occurred on agencies where BCG vaccine had been used as well as on agencies where vaccine was not used. For the first time we observed schoolrooms on Indian agencies without a single positive tuberculin reactor. This observation is in conformity with the observations throughout the world. It does not seem possible to indicate with confidence the cause or causes responsible for this marked decrease among these Indians.

In view of this rapid and marked decrease in the occurrence of tuberculosis in the United States and in other countries, it would appear inadvisable to vaccinate the general population with BCG vaccine. The logical policy outlined by the American Trudeau Society recommends the use of BCG vaccine for tuberculin-negative doctors, medical students, and nurses who are exposed to tuberculosis; all hospital and laboratory personnel whose work exposes them to the tubercle bacillus; persons who are unavoidably exposed to infectious tuberculosis in the home; patients and employees of mental hospitals, prisons, and other custodial institutions; tuberculin-negative children, and certain adults considered to have inferior resistance and living in communities in which tuberculosis mortality rate is unusually high.

Under no condition should BCG vaccination be regarded as a substitute for approved prophylactic measures used in the control of tuberculosis.

Summary and Conclusion

The value of BCG vaccine in the control of tuberculosis among eight American Indian tribes living in five widely separated areas has been investigated over a period of 20 years.

Tuberculin-negative school and preschool children grouped by age and sex were divided by alternation into two groups. A group of 1551 received an intracutaneous injection of BCG vaccine, while a group of 1457 received an intracutaneous injection of isotonic sodium chloride and served as controls.

In 1956, twenty years after the study was initiated, the areas were revisited and 1547, or 99.7%, of the vaccinated and 1448, or 99.4%, of the controls were accounted for. Of the BCG-vaccinated, 104, or 6.7%, had died of all causes during the 20 years of observation; 0.84% of tuberculosis; 3.0%, of nontuberculous disease, and 2.9%, of violence. Among the controls, 150, or 10.4%, had died of all causes; 4.7%, of

tuberculosis; 2.9%, of nontuberculous disease, and 2.9%, of violence.

The ratio of deaths from all causes of vaccinated to controls was 1:1.5; the ratio of deaths from tuberculosis was 1:5.2, and the ratio of deaths from nontuberculous disease and violence, 1:1.

Among the vaccinated, tuberculosis was responsible for 12.5% of all deaths, while among the controls, tuberculosis was responsible for 45.3% of all deaths.

In the control group the per cent of deaths from tuberculosis among females was twice as great as that among males, but in the vaccinated group the same per cent of both sexes died of tuberculosis.

Under the conditions of this study, a 15-year follow-up would have been sufficient to establish the value of BCG vaccine, since during the last quinquennium only one death from tuberculosis occurred among the vaccinated and three among the controls. Deaths from violence almost doubled in number in both vaccinated and controls during the last quinquennium.

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Hereditary Spherocytosis

Is the Duration of the "Aplastic" Crisis Influenced by Splenectomy?

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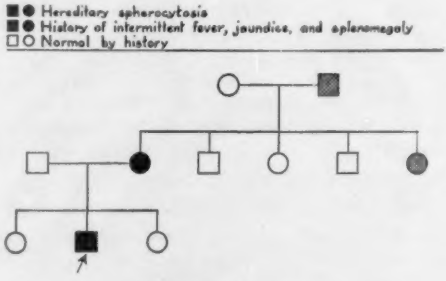
There is general agreement that hereditary spherocytosis is characterized by a chronic and continuous hemolytic process which results from an inborn error in the glycolytic metabolism of the spherocytes.[1,2] Whether anemia exists or not has been thought to reflect the ability of erythropoiesis to compensate for this increased and random destruction of red cells. The pathogenesis of the acute crisis, however, has been variously formulated. One generally held concept of the crisis visualizes a sudden increase in the rate of hemolysis.[3] The factors which might be responsible for this are still debated. In 1948, Owren reported the details regarding six cases of acute crisis in which the findings of anemia, thrombocytopenia, and reticulocytopenia were associated with hypoplasia of the erythroid elements in the bone marrow.[4] Owren questioned the concept of increased hemolysis and postulated that an "aplastic crisis" of the marrow accounted for the sudden fall in the erythrocyte count during crisis. In the same year, Dameshek and Bloom[3] reported seven cases of acute crisis where there were pancytopenia and reticulopenia but increased numbers of immature erythroid elements in the bone marrow. These authors suggested that an over-active spleen was responsible both for the increased rate of hemolysis and for a maturation arrest in erythropoiesis.

The present report is based on two patients, a mother and her son, both having hereditary spherocytosis and both studied during a severe "aplastic crisis." The two patients became ill within a week of one another. Each underwent splenectomy, the son after the advent of a spontaneous remission and the mother at the midperiod of the aregenerative phase. These two cases afforded an opportunity to see if splenectomy during crisis would shorten the duration of marrow erythroid aplasia.

Clinical Material

CASE 1.—A 7-year-old white boy was admitted acutely ill on May 28, 1957. His illness was of three days' duration and was characterized by the sudden onset of generalized weakness, chills and fever, nausea, vomiting and abdominal pain, and the development of marked pallor. The mother stated that the child had had several previous attacks similar to but less severe than the present illness. She stated that the patient had had "yellow eyes" all of his life and that he was known to have an enlarged spleen. The relevant family history is illustrated in the Figure. At the time of admission the boy appeared severely ill. The temperature was 102 F; pulse, 130 per minute;



Pedigree of family.

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TABLE 1.—*Laboratory Data—Son*

Days After Onset of Crisis	RBC, 10^3/Cu. Mm.	HCT, %	HB., Gm./100 Cc.	Reticulocytes %	Reticulocytes 10^3/Cu. Mm.*	Marrow Aspirate Pronormoblasts, %	Marrow Aspirate Normoblasts, %	WBC, 10^3/Cu. Mm.	Indirect V. D. B., Mg./100 Cc.	Comments
4	2.1	8	3.8	0.8	17	3	0	4.4	4.0	1000 cc. whole blood
5	2.5	22	7.9	0.6	15			7.1		500 cc. whole blood
6		32	10.3	0.6				7.7		
7			9.4	0.2				2.6		500 cc. whole blood
8		31	10.6	0.8				7.5		
11	3.0		10.8	3.7	111			9.9	0.4	Serum iron, 230
12						1	32			
18	3.6	31	10.0	0.4				8.3		
21	3.1		9.0	0.3						
27				Splenectomy						Transfused
28	3.7		14.1	6.0	222			25.3		
31	4.2		13.0	2.0				12.0		
34	4.6	38	14.0	0.9						

* % reticulocytes×RBC.

respirations, 30 per minute, and blood pressure, 118/60/0. The skin was clammy, and there was evidence of air hunger. Additional findings included pallor, distinct scleral icterus, no lymphadenopathy, and a relaxed abdomen, with the liver edge felt 2 cm. below the costal margin and the edge of the spleen felt 8 cm. below the rib cage on the left. The pertinent laboratory data are presented in Table 1. The initial hematocrit reading was 8%. There was a reticulocytopenia, and the stained smears of the peripheral blood showed marked microspherocytosis. The erythrocytes exhibited increased osmotic fragility, and the Coombs' test was negative. The bone marrow aspiration was remarkable in that it showed no normoblasts and only 3% pronormoblasts. The total bilirubin was 5.0 mg. per 100 cc., with an indirect-reacting fraction of 4.0 mg. The urine contained increased urobilinogen.

Whole-blood transfusions given immediately following admission produced symptomatic improvement. The child showed spontaneous clearing of jaundice and the beginning of a reticulocytosis on the 11th day after the onset of the crisis. The next day the bone marrow showed evidence of normoblastic hyperplasia. The height of the reticulocytosis was inadvertently missed. The subsequent course was uneventful. An elective splenectomy was performed on the 27th day after the onset of the crisis, which was approximately 2 weeks after the spontaneous remission of the aregenerative phase. The postoperative course was smooth. The patient was discharged nine days after splenectomy. At this time he was asymptomatic and the blood values were normal. The erythrocytes continued to show increased osmotic fragility.

The spleen weighed 450 gm., and there were numerous accessory spleens. The capsule showed fibrinous adhesions, and the parenchyma was firm on cut section. With hematoxylin and eosin staining the follicles were very prominent, with distinct germinal centers. The sinusoids were dilated, and the lining endothelial cells appeared hyperplastic. No erythrophagocytosis was observed. A few areas showed iron encrustation, and there was no increase in hemosiderin. Silver staining showed no unusual reticulum network. The combined stain of Rinehard and Abul-Haj showed a striking prominence of the basal membrane of the sinusoids. The total

TABLE 2.—*Laboratory Data—Mother*

Days After Onset of Crisis	RBC, 10^3/Cu. Mm.	HCT., %	HB., Gm./100 Cc.	Reticulocytes %	Reticulocytes 10^3/Cu. Mm.*	Marrow Aspirate Pronormoblasts, %	Marrow Aspirate Normoblasts, %	WBC, 10^3/Cu. Mm.	Platelets, 10^3/Cu. Mm.	Indirect V. D. B., Mg./100 Cc.	Comments
4	1.1	7	2.9	5.3	58	5	0	4.9	340	3.9	1500 cc. whole blood
6	2.0	29	6.9	5.5		2	3	4.4	155	1.9	BUN 80 mg./100 cc.
				Splenectomy							Transfused
6						3	2				
7	2.2	23	7.2	0.1		8	6	9.2	90	1.1	Uric acid 12.0 mg./100 cc.
8				0.0							
9		22	7.7					27.3			
10	2.1	22	6.7	1.1	23			30.4	720		Cholesterol 90 mg./100 cc.
11	2.1	22	6.4	5.1	102	3	53	33.7		1.2	Uric acid 7.5 mg./100 cc.
12	2.8		7.5	9.9							
13	2.8			11.2							
14	3.0	30	9.1	12.0	360			13.9		1.1	BUN 14 mg./100 cc.
18	2.9	32	9.4	5.1				12.2			

* % reticulocytes×RBC.

microscopic picture of this spleen was one which was indistinguishable from that seen in many cases of idiopathic thrombocytopenic purpura.[5]

CASE 2.—The mother of the first patient, a 27-year-old white woman, was admitted acutely ill on June 4, 1957. Her illness had been sudden in onset, beginning four days prior to admission. It was characterized by profound weakness, chills and fever, nausea, vomiting, abdominal discomfort, and the development of profound pallor. She gave a history of similar but less severe episodes occurring throughout her life and estimated that she was incapacitated some six months of each year. She had long been known to be anemic and on numerous occasions had been told that her spleen was enlarged. On admission the patient was confused and obtunded and was considered critically ill. The temperature was 100 F; pulse, 120 per minute; respirations, 18 per minute, and blood pressure, 90/40. The skin was cool, moist, and pale. There was icterus of the sclerae, and the mucous membrane was pale. The heart was unremarkable except for a sinus tachycardia and a precordial systolic murmur. There were no pulmonary rales. The liver edge was palpated 4 cm. below the right costal margin, and the spleen, 10 cm. below the left. Neither organ was unusually tender. The pertinent laboratory data are given in Table 2. The initial hematocrit reading was 7%; the white cell count, 4900 per cubic millimeter; platelets, 340,000 per cubic millimeter, and reticulocytes, 5.3%. Microspherocytes characterized the peripheral blood. The erythrocytes showed increased osmotic fragility to hypotonic saline, and the Coombs' test was negative. The indirect-reacting bilirubin value was elevated. As in the first case, on aspiration the bone marrow showed as its only abnormality a reduction in erythropoiesis, with only 5% pronormoblasts.

Whole blood, 1500 cc., was transfused, and the patient showed remarkable symptomatic improvement. Since it seemed clear that this patient, like her son, was in an aregenerative crisis, it was recognized that she presented an ideal opportunity to evaluate the effect of splenectomy on the duration of the normoblastic hypoplasia. Accordingly, a splenectomy was performed on the sixth day after the onset of the crisis. The postoperative course was entirely uneventful. There was a prompt decrease in the patient's jaundice, and this was confirmed by a fall in the van den Bergh test. It was interesting that these changes preceded the development of a reticulocytosis by five days. Like her son, this patient first showed a reticulocytosis on the 11th day after the onset of the crisis. It reached its peak on the 14th day. At the time that the reticulocytosis was observed in the peripheral blood, the marrow exhibited a dramatic normoblastic hyperplasia. When discharged three weeks after admission, the patient stated that she felt better than she had in years.

The spleen weighed 950 gm. The capsule was tough and fibrous. Sections stained with hematoxylin and eosin showed spotty thickening of the capsule. The follicles were decreased in size and number, and no germinal centers were visible. Sinusoids were gaping, and the lining endothelium was hyperplastic. The dilated sinusoids were mostly devoid of blood, but there was congestion of the interstitial tissue. There was no increase in hemosiderin, and no erythrophagocytosis was observed. Small foci of iron encrustation were seen in the trabeculi. The silver stain showed an increase in the number and coarseness of the reticulum fibers. The combined stain revealed nothing of note, and the picture differed in this regard from that seen in the spleen of her son.

Comment

The fundamental defect in hereditary spherocytosis seems well established as an inborn error in the carbohydrate metabolism of the erythrocyte.[2] As with other hereditary hemolytic anemias, the phenomenon of the crisis, i. e., rapidly progressive anemia, must be the result of either increased erythrocyte destruction or decreased red cell delivery or a combination of both factors. Despite varying reports in the literature, it is clear that many cases which have been studied early in crisis have shown aplasia of marrow erythropoiesis, and some would imply that all crises are so characterized.[4,6-9] High levels of urinary and fecal urobilinogen have been interpreted as evidence for an increased rate of hemolysis during crisis. The logic of this inference has been challenged,[10] and the range of values seen during crisis are at times no higher than those gotten during quiescent periods of the disease. Using cross transfusion techniques, Singer et al.[11] felt that the calculated loss in circulating erythrocytes in sickle-cell disease was the same whether or not the patient was in crisis and that the transient marrow failure could account for the anemia without assuming hyperhemolysis. At present it would seem unwise to exclude the possibility that more

than one mechanism may be responsible for the crisis.

In hereditary spherocytosis, the spleen certainly plays a mechanical role in the accelerated removal of the defective red blood cells from the circulation.[13] The success of splenectomy in treatment further supports this concept. The "trigger mechanism" for the crisis is obscure, and a variety of mechanisms have been suggested.[12] As has been noted previously, Dameshek and Bloom have suggested that the spleen elaborates a humoral factor which inhibits the release of formed elements from the marrow.[3] Were this type of hypersplenism a major mechanism in the crisis, early splenectomy might be expected to shorten the period of bone marrow aplasia and speed the development of the reticulocytosis.

The cases reported here have two features which make them germane to the above considerations. Both cases illustrate well an aregenerative phase of erythropoiesis during a period of rapidly progressive anemia. The cases of "aplastic" crisis previously reported have been rather consistent in that the aregenerative periods preceding reticulocytosis have lasted from 10 to 14 days.[12] The son followed this pattern and can be considered as a fair control for his mother. The mother, therefore, afforded us the opportunity to test the hypothesis that the spleen might play a causative role in the erythropoietic hypoplasia. It was reasoned that if the spleen elaborated a hormone-like substance which produced a maturation arrest in the marrow early splenectomy might result in an earlier reticulocytosis. In the mother, splenectomy was performed on the sixth day of crisis. Immediately thereafter there was the expected fall in serum bilirubin. The myeloid and megakaryocytic activity of the marrow responded to splenectomy in the expected fashion. However, there was no dramatic change in the degree of erythroid activity in the bone marrow or in the level of the circulating reticulocytes. As in her son, these developments made their appearances between the 9th and 14th days after the onset of the crisis. It is to be emphasized that all bone marrow aspirations examined in both patients were considered normal as to cellularity, myeloid activity and maturity, numbers of megakaryocytes, and platelet production. This latter is specifically mentioned, since the mother showed a transient thrombocytopenia. It was concluded, therefore, that the splenectomy in the mother's case did not influence the duration of the "aplastic" crisis.

Summary

Two cases of hereditary spherocytosis, a mother and her son, were studied during severe "aplastic" crises.

In each patient, the crisis was characterized by profound anemia, reticulocytopenia, and depressed erythropoiesis in the bone marrow.

In the son, splenectomy was performed during a quiescent period following a spontaneous remission. In the mother, the splenectomy was performed on the sixth day of crisis. The duration of normoblastic aplasia was approximately 12 days in both cases.

On the basis of these findings, the causative role of the spleen in the precipitation and maintenance of the "aplastic" crisis is questioned.

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Acute Glutethimide (Doriden) Poisoning

The Use of Bemegride (Megimide) and Hemodialysis

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Glutethimide (Doriden)* has had an unusually rapid and widespread introduction into clinical medicine as a hypnotic and sedative. Chemically, glutethimide is α-ethyl-α-phenylglutarimide whose structual formula is depicted in Figure 1. It is a white crystalline compound with a melting point of 83-85 C and a molecular weight of 217.3. It is very poorly soluble in water but highly soluble in alcohol and acetone. In large doses, the gastric absorption may be irregular and produce variations in the LD_{50} obtained after oral administration in animals (0.6 gm. per kilogram in the rat and rabbit, 0.5 gm. per kilogram in the dog, and 0.15 gm. per kilogram in the mouse). The problem of absorption also makes it difficult to establish dose-toxicity relationships in human glutethimide poisoning. Once absorbed, glutethimide is eventually excreted in the bile, and up to 85% can be recovered from a biliary fistula.[1] It is presumably available for reabsorption from the intestine and is then excreted in the urine as a conjugate or metabolite.[2] Working with C^{14} ring-labeled glutethimide, Bernard et al.,[1] found that in 15 hours 40% had been eliminated from the body, 34% remained in the intestinal tract, and the residual was distributed in body tissue, with 0.1% in brain and spinal cord.

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* Developed by Ciba Pharmaceutical Products, Inc., Summit, N. J.

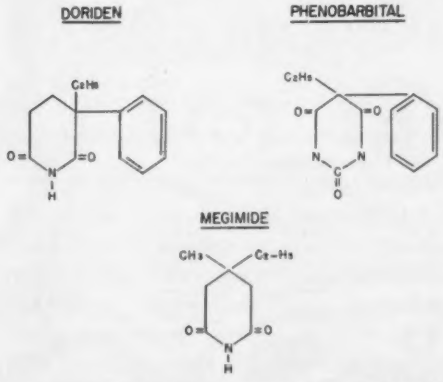

Fig. 1.—Chemical structures of glutethimide (Doriden, α-ethyl-α-phenylglutarimide) phenobarbital, and bemegride (Megimide, β-methyl-β-ethylglutarimide).

While working with a new barbiturate antidote,[3] β,β-methylethylglutarimide † introduced by Shaw et al.,[4-6] we were stirred by the clinical similarity (Fig. 1) and disparate pharmacology of α-ethyl-α-phenylglutarimide, the depressant, and β-methyl-β-ethylglutarimide, the stimulant. Shortly thereafter, we had the opportunity of contrasting the response to glutethimide in barbiturate poisoning to the clinical response in a patient who was admitted with presumed barbiturate intoxication but proved subsequently to have negligible amounts of barbiturate and a substantial concentration of glutethimide in the serum.

† Supplied by A & G Nicholas, Ltd., 1 Park Ave., New York 16.

The present study summarizes our experience in six cases of severe acute glutethimide poisoning which were managed with varying combinations of supportive measures, bemegride (Megimide), and external hemodialysis. There was one fatality which we believe would have been preventable with our present knowledge.

Materials and Methods

All patients were admitted to the medical service of Georgetown University Hospital. Glutethimide was identified and measured in the serum by the method of Goldbaum, Williams, and Koppanyi.[7] β,β-methylethylglutarimide was administered in a dilute solution of 5.0 mg. per milliliter, which was injected into the tubing of a running intravenous infusion of 5% dextrose in distilled water. Ten milliliter increments were injected over a 3- to 5-minute period, with 10 to 15 minutes between doses. The injection was stopped when a satisfactory lightening of anesthesia was obtained, as evidenced by good respiratory excursions and return of reflexes. The plantar withdrawal was considered to be the single most valuable sign. Injection was also stopped when excessive grimacing, muscle twitching, or clonus heralded the danger of convulsions. Reflex changes were graded on a scale of 0 to 5 and when presented in serial fashion represent the judgment of a single observer. Since both plantar withdrawal and pain response may exhibit reinforcement on rapidly successive testing, the maximum response was consistently chosen for recording.

External dialysis was carried out in the renal laboratory, with use of a Kolff-Brigham rotating dialyzer. Associated barbiturate levels which are measurable in serum without interference from glutethimide were determined by the method of Goldbaum.[8]

Presentation of Cases

CASE 1.—A 31-year-old white septigravida tertipara housewife was admitted in coma via ambulance at 10 a. m. She had been found unresponsive by her husband six hours previous to admission. She was believed to have taken 7.5 gm. of glutethimide nine hours previous to admission. Gastric lavage was attempted in a community hospital but produced apnea and cyanosis on attempted passage of the nasal tube. She was then transferred to Georgetown University and admitted directly to the renal laboratory.

Past history was significant for marital and psychiatric difficulty. She had visited a psychiatrist on two occasions and had been advised to have further psychiatric care. She had been given separate prescriptions for two brands of meprobamate (Equanil and Miltown [2-methyl-2-n-propyl-1,3-propanedial dicarbamate]) and glutethimide. Blood pressure was 92/60; rectal temperature was 98.8; pulse was 76 per minute, and the respiratory rate was 18, with shallow abdominal breathing. The patient appeared completely flaccid, with no deep tendon, plantar-withdrawal, corneal, or light reflexes. There was no response to painful stimuli. The initial glutethimide blood level was 2.8 mg/100 ml., and no barbiturate was present. Oxygen was given by nasal tube, and a 500 cc. infusion of 5% dextrose in water was begun. The patient was then titrated with a total dose of 900 mg. of bemegride over a two-hour period. The details of the response to bemegride are presented in Table 1. After titration with bemegride, the glutethimide blood level was 4.1 mg/100 ml. and the patient was showing spontaneous movements, was sobbing, and was able to answer a few questions. She admitted at this time to the ingestion of "several" tablets of meprobamate and "several" tablets of glutethimide. She remained in a satisfactory state of light anesthesia throughout the afternoon but showed some signs of re-

TABLE 1 (Case 1).—*Serial Clinical Signs in Relation to the Cumulative Intravenous Dose of Bemegride* *

	Total Dose of Bemegride I. V., Mg.				
	0	150	400	550	900
Reflexes					
Corneal	0	0	++++	++++	++++
Light	0	±	+	++++	++++
Knee	0	0	±	++	++
Ankle	0	0	±	+++	+++
Plantar withdrawal	0	±	+++	++++	++++
Pain response	0	±	±	++++	++++
Blood pressure	92/60	100/72	100/76	100/70	95/60
Pulse	76	68	80	76	76
Respirations	18	22	22	24	22
	Abdominal	Thoracic			
Blood level, mg./100 ml.	2.8				4.1
Remarks				Spontaneous movements	Talking
Running time, min.	0	10	20	45	105

* Patient ingested 7.5 gm. of glutethimide 9 hr. before treatment. Bemegride was given in 50 mg. increments every 3–5 min.

gression by late evening. At approximately 10 hours after the initial titration, the patient became unresponsive and had a marked decrease in the previous deep tendon reflexes. The blood pressure, pulse, and respiration, however, remained satisfactory. Twenty-four hours later, the patient still did not respond to painful tendon reflexes and could be aroused to the point of jumbled speech. Thirty hours later, the patient developed hyperpyrexia, with a rectal temperature rising to 104.8 F (a common finding in glutethimide poisoning). Respirations were rapid at 40 and shallow. There was a sinus tachycardia at 120 per minute. Breath sounds were decreased at the right base posteriorly, but lungs were dry. The x-rays showed nodular areas of increased density together throughout the entire right lung field. The rest of the lung structure was normal. Leukocyte count was 16,000, with 89% polymorphonuclear cells and 8% band cells. The throat smear revealed Gram-positive cocci, and an α-Streptococcus was cultured. Therapy with antibiotics was started, with a reduction of temperature and leukocytosis by the third hospital day. Although remaining hazy, for 48 hours, the patient was alert and cooperative, with normal vital signs and gradual clearing of her sensorium. She was discharged to psychiatric care on the sixth hospital day. In addition to the initial dosage of bemegride, she required additional small increments as follows: 25 mg. at two hours, 25 mg. at two and one-half hours, 25 mg. at four hours, 50 mg. at four and one-half hours, and 25 mg. at four and three-quarters hours. Although there was some regression between seven and nine hours, it was not considered necessary to give any additional bemegride. In a subsequent psychiatric interview, the patient described a partially lucid interval in her coma which apparently corresponded to the initial bemegride titration. She described that she heard people in a room talking. She described them in terms of hallucinations, but these were not rigidly believed-in hallucinations. While they seemed unreal, they did not disturb her. She had no awareness of being depressed or crying, which was the outward reaction to her initial awakening with bemegride.

Comment.—This patient had severe glutethimide poisoning from the ingestion of 7.5 gm. Possible synergism of meprobamate cannot be assessed. Apnea on intubation was a disturbing complication and is unusual in similar degrees of barbiturate intoxication. Poor ventilation was a function of shallow breathing rather than depressed respiratory rate. The clinical response to bemegride was direct, dramatic, and sustained only by small doses of the drug. The febrile episode could have been due to glutethimide per se or to an aspiration bronchopneumonia and might have been of serious prognostic import were it not for the restoration of cough reflexes and consciousness.

CASE 2.—A 36-year-old white woman was admitted to the hospital in coma. She was found unconscious on the day of admission and had last been seen in a conscious state some six hours before. Several empty bottles were found in her room. Investigation of the prescription dates and quantities suggested that she had taken approximately 10 gm. of glutethimide and possibly a small amount of secobarbital (Seconal). Past history revealed irregular menstrual periods and a disability rating for psychoneurosis. She had a previous hospital admission for a generalized "neurodermatitis" and a history of migraine headaches. Marital difficulties preceded the present suicidal attempt. Physical examination revealed a well-developed well-nourished white woman who was deeply comatose. The blood pressure was maintained with levarterenol (Levophed) at a level of 130/80 and on withdrawal would fall rapidly to 90/60. The pulse ranged from 68 to 72; respirations were 4 to 6 per minute and were extremely shallow. There were no corneal, light, gag, cough, or deep tendon reflexes or response to painful stimuli. She was completely flaccid and comatose. There were small areas of neurodermatitis on the legs. Initial therapy was intravenous 5% dextrose and water, caffeine, pentylenetetrazol (Metrazol), intratracheal oxygen, suction of secretions, penicillin, and continuous intravenous levarterenol. Blood taken at this time revealed a glutethimide level of 2.6 mg/100 ml. and a barbiturate level of 1.0 mg/100 ml. Approximately three hours after admission titration was begun with bemegride and amiphenazole (Daptazole). A total dose of 350 mg. of bemegride and 350 mg. of amiphenazole was given. There was a definite response in deep tendon reflexes and a dramatic response in respiratory rate. At this time the drugs were in short supply and the entire available amount had been depleted. The patient showed some regression of deep tendon reflexes and was transferred to the Walter Reed Army Medical Center, where she underwent a successful external hemodialysis and recovered.

Comment.—The depression of respiratory rate in this patient was extreme and atypical in experience with glutethimide poisoning. It may have been related to the associated barbiturate or ingestion of alcohol or some other unknown drug. The response to a

limited dose of bemegride was immediate and dramatic. The exhaustion of our supply of bemegride and clinical regression of the patient prompted our recommendation of external hemodialysis. Amiphenazole (Daptazole), which is 2:4-diamino-5-phenylthiazole hydrobromide or hydrochloride, was originally employed in combination with bemegride.[5] It is a nonspecific respiratory stimulant, and while it may have been of value in this particular case of marked respiratory depression, we have preferred to study bemegride alone in subsequent cases of barbiturate and glutethimide poisoning.

CASE 3.—A 24-year-old white woman was admitted unresponsive after the ingestion of 10 gm. of glutethimide on the day of admission. Her husband had telephoned home at 4 p. m. and at 6 p. m. and received no response. On arriving home at 10 p. m., he found the patient unresponsive beside an empty bottle which had contained 20 tablets (0.5 gm.) of glutethimide. In addition, there were available to her hydroxyzine hydrochloride (Atarax, 1-[*p*-chlorbenzhydryl]-4-(2-[2-hydroxyethoxy] ethyl) piperazine dihydrochloride) and chlorpromazine (Thorazine), and there was a distinct odor of alcohol on her breath. She was admitted to her community hospital, where physical examination revealed her to be in shock and deep coma. There were no corneal, light, or gag reflexes or any response to deep tendon reflexes or painful stimuli. Blood pressure was 68/0, and the pulse was weak. The patient was lavaged until the returns from the tube were clear and was given levarterenol and caffeine and intratracheal suction was done. Blood pressure was brought up to 120/80, and she was transferred to our hospital at 11:30 p. m. Past history revealed an accidental shot gun injury to the chest at the age of 6. She had a manic-depressive personality and had made one previous suicide attempt with bartiturates. The patient was totally unresponsive and flaccid, with shallow abdominal respirations and widely dilated pupils, and was areflexic. Blood pressure was 110/70 during therapy with levarterenol, and the pulse was 78 per minute. The heart and lungs were normal.

Leukocyte count was 18,450 with 73% polymorphonuclear cells, 2% band cells, 12% mononuclear cells, and 14% lymphocytes. Hematocrit was 44; hemoglobin, 14 gm. The glutethimide level at this point was 4.0 mg/100 ml. The patient was titrated with a total dose of 2.75 gm. of bemegride, which produced an improvement in breathing and restoration of plantar-withdrawal, light, corneal, ankle- and knee-jerk reflexes and slight pain response. It also produced two typical grand mal convulsions without incontinence appearing during intervals immediately after the administration of the drug. There was always regression of the patient's coma within a few minutes after administration of bemegride. Details of the bemegride titration are presented in Table 2 together with changing values of the blood glutethimide level. She was returned to the ward with good corneal and light reflexes and satisfactory plantar withdrawal. Blood pressure was well maintained with very small amounts of levarterenol. The patient was considered to be in a light state of anesthesia. She remained in a satisfactory condition, with relatively deep coma but constantly present plantar-withdrawal, light, and corneal reflexes; pain response, and even a faint cough reflex for approximately 24 hours. At 36 hours the patient was noted to have good light and corneal reflexes, a 1+ knee jerk, 2+ ankle jerk, and a repeated withdrawal on plantar stimulation. At 40 hours she again regressed, with diminution

TABLE 2 (Case 3).—*Serial Clinical Signs in Relation to the Cumulative Intravenous Dose of Bemegride* *

	Total Dose of Bemegride I. V., Mg.					
	0	450	1,500	2,150	2,500	2,500
Reflexes						
Corneal	0	+	++	++	+	+
Light	0	+	++	+	+	+
Knee	0	0	0	0	+	0
Ankle	+	+	+	+	+	+
Biceps	0	0	0	0	0	0
Cough	0	0	0	0	+	0
Plantar withdrawal	0	±	+	+++	++	0
Pain response	0	0	0	0	0	0
Blood pressure	100/90	110/90	110/60	130/60	120/80	110/40
Pulse	88	96	72	86	120	84
Respirations	18	18	20	18	24	18
Blood level, mg./100 ml.	Abdominal 4.0	Thoracic	Deep			5.4
Remarks	Deep coma, pupils dil.	Deep coma	General convulsion	Deep coma	Groaned, coughed	Convulsion regressed
Running time, min.	0	10	34	90	135	190

* Patient ingested 10 gm. of glutethimide plus alcohol and chlorpromazine 7 hr. before treatment. Lavage and caffeine failed. O_2 and levarterenol continued. Bemegride given in 50 mg. increments.

of corneal reflexes, and she required an additional 25 mg. of bemegride, which produced an immediate improvement in her level of anesthesia. At 44 hours from the time of ingestion, the corneal reflexes disappeared, the pupils were dilated, and the patient appeared more anoxic. She was given an additional 200 mg. of bemegride, at which time the corneal reflex returned. There was a slight spontaneous movement of her feet and hyperventilation. At 65 hours, it was noted that the patient was breathing without difficulty. Blood pressure was 124/70 without levarterenol. The patient had excellent plantar withdrawals and appeared to be very responsive to stimuli. However, her deep tendon reflexes had regressed and had not returned following the previous bemegride dosage. A good cough reflex was noted. At this point the patient had an episode of irregular and difficult breathing which improved on deep suction of the trachea. At approximately 67 hours, she appeared to be in light coma and in a satisfactory condition. She was taken to be weighed. While being transferred from the litter she suddenly became apneic and cyanotic. She was returned to bed and given oxygen, and spontaneous respiration began. However, the patient remained cyanotic with dilated pupils. Blood pressure, which had been 120 a few minutes before this episode, fell to 0. Deep suction was unsuccessful, and an intratracheal tube was inserted with positive-pressure oxygen. No pulse could be obtained or heart sounds heard. The chest was opened, and with the use of levarterenol and cardiac massage, the heart beat was transiently restored. Efforts were made to maintain it with a pacemaker, but no spontaneous contractions occurred, and the patient was declared dead at 69 hours. Postmortem examination revealed the following findings. Respiratory system: pulmonary congestion and edema; multiple healed granulomata, nonspecific, in the subpleural area, left lower lobe; adhesive pleuritis, right lung; atelectasis, left lower lobe; mucus plug, right lower-lobe bronchus. Cardiovascular system: foreign body; 2 mm. metallic fragments were found in the pericardium, epicardium, and myocardium. There was fatty degeneration of the heart. There was marked coronary arteriosclerosis, with virtual occlusion of the left anterior descending branch, aortic arteriosclerosis, mild sclerosis of the mitral valve. Digestive system: focal fatty metamorphosis of the liver, focal hemorrhage of the liver, calcific mesenteric lymphadenopathy, ulcer of the colon. Urogenital system: congestion of the kidney, hemorrhagic cystitis, multiple follicular cysts of ovary, leiomyofibroma uteri, corpus luteum, involuting, and proliferative endometrium. Endocrine system: atrophy of thymus gland, multiple adrenal cortical adenomata. Brain: cerebral edema. This is reported to be a consistent finding in patients who die suddenly from glutethimide intoxication.[26]

Toxicology Comment.—The stomach contents were green and thick, containing suspended particles of white undissolved material resembling pieces of glutethimide tablets. There was one tablet with fairly sharp edges which was almost completely undissolved. The gastric mucosa showed a normal rugal pattern with a few petechiae. There was no evidence of ulcer. The gastric contents were removed, dissolved in alcohol, and found to contain more than 675 mg. of glutethimide.

Comment.—There seems little doubt that this fatality occurred as a result of several unfavorable features. The patient had ingested alcohol, which is known to markedly potentiate the absorption and toxicity of glutethimide. The patient also had a pigmented material in her stomach resembling the coating of a chlorpromazine tablet, and there was some probability that she had ingested hydroxyzine hydrochloride. It is possible that both of these agents might potentiate the toxic effects of glutethimide. Despite an apparently adequate lavage, it was clear that large amounts of glutethimide remained undissolved in the gastric contents, and probably reabsorption from the gastrointestinal tract could account for her frequent regression from a satisfactory clinical state. Cyclic variation in glutethimide anesthesia has been noted in animals. Since the patient had widely dilated pupils, it is unknown whether the initial shock episode had produced a major degree of cerebral anoxia. Lastly, the patient's death occurred suddenly during exertion at a time when the general anesthetic level was good. The final mechanism of death seemed to be apnea with cardiac standstill. A surprise finding at autopsy was the presence of a massive coronary atherosclerosis, which must be considered most unusual in a 24-year-old woman. The anterior descending branch of left coronary artery was markedly atherosclerotic, with a pinpoint lumen, and one branch of the artery was totally occluded.

There was thickening along one edge of the mitral valve. Within the epicardial fat, the pericardium, and in the myocardium itself were several small lead shots imbedded in tissue, without surrounding inflammatory reaction, representing a residual from a childhood shotgun blast. It is possible that this traumatic injury to the coronary vessels could have predisposed to the extraordinary degree of premature atherosclerosis. We can only speculate on whether circulatory impairment could have contributed to her mode of death. No actual infarction was demonstrable. Cerebral edema was present, but there was no herniation.

CASE 4.—A 44-year-old white woman appeared sleepy the night before admission and on the morning of admission was noted to be staggering and stumbling about the house, where she fell unconscious in the late morning. In the afternoon she was seen by a doctor, and she was transferred to the hospital at 6 p. m., which was believed to be 12 hours after ingestion of glutethimide. The exact amount of glutethimide ingested is not certain. A prescription was filled approximately 10 days previous to admission for 24 tablets, and it was estimated that 12 of these were taken during the succeeding 10 days, so that the patient probably took at least 6 gm. acutely superimposed on whatever residual blood level she had. A second unlabeled empty vial was also found.

Past history: Patient has been a known manic depressive for the past 16 years. Fourteen years ago she made an attempt at suicide with unknown drugs. She had been under psychiatric care in the interim and had swung through cycles of mania and depression. During the past summer the patient was in an elated mood, but in the recent months she had shown progressive depression. On examination the patient was a well-developed white woman in a comatose state, with flaccidity of all skeletal muscles. The blood pressure was 134/85. The pulse was 92 and regular. The respirations were 24, loud and snoring. There was an element of spasticity in the left arm in extension. The neck was supple. The pupils were widely dilated but reacted to light. There was a suprapubic movable firm mass about 3×3 cm., thought to represent a uterine fibroid. The corneal, biceps, knee, and Achilles reflexes were totally absent. There was a slight response to painful stimulation. Gag and cough reflexes were present.

Course: Since the patient had not previously been lavaged and the exact time of ingestion was unknown, an Ewald tube was passed. At the beginning of the attempt, a period of apnea resulted. Respiration was resumed immediately after cessation of the attempted passage of the tube. After a 10-minute waiting period, a second passage was tolerated well and the stomach was successfully lavaged. At the end of this procedure, the patient again became apneic, cyanotic, and tense and went into extensor spasms. There was no coughing. This lasted about 30 seconds. The tube was rapidly removed. She was given artificial respiration but remained apneic for a period of two minutes. Gasping respirations were then resumed and were much shallower than previously. Her blood pressure dropped to 30/0. She was placed in a shock position, and an intratracheal tube was inserted. During the intubation about 500 ml. was vomited. The respirations continued to deteriorate to shallow abdominal breathing. She lost all pupil reactivity and response to pain. She was unable to maintain her blood pressure in the shock position, and it fell to levels of 85/0 or 55/0, at which time levarterenol administration was begun and produced a good pressure response. Because of the deteriorating clinical condition, the patient was taken directly to the kidney laboratory for external hemodialysis.

Dialysis note: The left brachial vein and artery were cannulated, and the patient was connected to a rotating Kolff-Brigham artificial kidney at 9:50 p. m., approximately four hours after admission. She required continued levarterenol infusion through an inferior vena caval catheter, and the blood pressure was maintained at 120/80. Respirations were abdominal at 24 per minute. She had no deep tendon reflexes, had no light reflex, and had a barely perceptive pain response on repeated stimulation. During the next four hours she progressed to a lighter state of anesthesia. The dialysis was technically satisfactory, with flow rates averaging between 200 and 320 ml. per minute. Dialysis was continued for 4 hours 20 minutes. At the end of that time, there were 2+ light reflexes, 3+ corneal, 3+ cough and gag, 4+ knee jerk, 2+ ankle jerk, and 2+ plantar withdrawal. She reacted to supraorbital pressure with groaning speech. She had thoracic respirations at 30 per minute and 2+ biceps response. The blood pressure was well maintained without levarterenol after the first two hours of dialysis. During the removal of the cannulas and suture of the skin, she reacted with agitated movements and appeared about ready to wake up. However, she did not talk or have any coherent purposeful movements. She was returned to her room in good condition. The details of changes in blood level during dialysis are presented in Figure 2. Further hospital course: Twenty-four hours after admission, the patient again regressed clinically and became dependent upon levarterenol, with a fall in blood pressure to 86/50. She was then

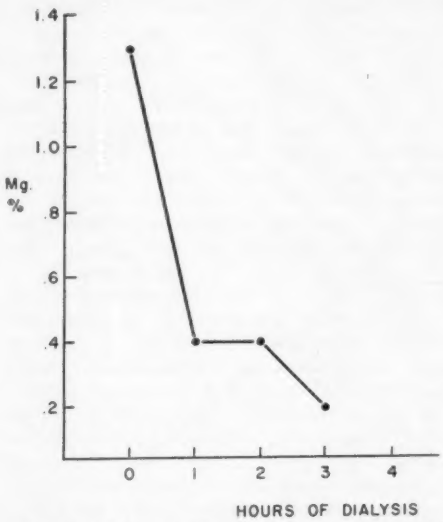

Fig. 2 (Case 4)—Change in measured blood concentration of glutethimide during external hemodialysis.

given 50 mg. of bemegride intravenously, with transient elevation of the blood pressure to 110/60. She was then given three successive 50 mg. doses at 10-minute intervals and each time responded with a transient pressor effect to the same range of 110/60, with the blood pressure dropping back each time to systolic pressure of 70 to 80/40 to 50 without levarterenol. After 200 mg. of bemegride, the patient was much more alert, had spontaneous movements, and began to appear quite restless. She still required levarterenol for satisfactory blood pressure. Bemegride was continued in small doses over a period of approximately one and one-half hours. After the total accumulative dose of 350 mg., the patient began to speak, complained that she didn't want to wake up, and asked us to stop giving her this medicine. She remained in a good satisfactory condition subsequent to this, except for transient drops in blood pressure to levels of 85 to 90/60, which required intermittent use of levarterenol. No more bemegride was required, and the following day the patient, while still appearing depressed and self accusatory, was nevertheless irritable and able to sit up. Temperature rose to 101.5 F on the second hospital day and gradually subsided to normal. The patient made a satisfactory response and was discharged to psychiatric care on the 12th hospital day. There were albumin and acetone in the initial urine on admission, which gradually disappeared with hydration and feeding. The hematocrit was 38. The white cell count was 19,000, with 28 lymphocytes, 70 polymorphonuclear cells, and 2 band cells. Icteric index, 10; total eosinophil count, 0. Blood urea nitrogen was 7 mg/100 ml.; CO_2 combining power, 47 vol.%; calcium, 9.4 mg/100 ml.; K, 3.5 mg/100 ml., and phosphate, 3.9 mg/100 ml. Electrocardiogram showed a sinus tachycardia and prolongation of the Q-T interval.

Comment.—This patient demonstrated a marked hypotension, which continued even after return of a reasonable degree of consciousness. There was also the possibility of chronic cumulative toxicity of glutethimide, since she appeared groggy before her acute ingestion. She demonstrated apnea on manipulation, which was also seen in Cases 1 and 3. Anoxemia worsened the coma, and this patient might not have survived without hemodialysis, which reduced the blood glutethimide level.

CASE 5.—A 47-year-old white man was transferred to this hospital because of suspected glutethimide intoxication. He was unemployed and had been consuming heavy amounts of alcohol for the past three to four years owing to periodic depressions resulting in the loss of his job six months previously. This was followed by an exacerbation of his depression, and on two previous occasions he was known to have taken mild overdoses of barbiturates. He had been under psychiatric therapy but continued to drink heavily. The family seemed quite certain that he had little or no alcohol in the 48 hours preceding the ingestion of glutethimide. Approximately 12 hours previous to admission, he took a reported dose of 24 tablets (0.5 gm. each) of glutethimide, or 12 gm. He was found in a comatose state and transferred to the hospital. Past history was positive for an appendectomy five years ago, peptic ulcer five years ago, and probably cholelithiasis. The family history was not contributory. On examination the blood pressure was 110/70. The pulse was 100 per minute, and the respirations, 20 per minute, with occasional periods of Cheyne-Stokes breathing. The patient was a well-developed well-nourished obese white man who showed restless movements but was otherwise comatose. Muscle tone was increased in response to vocal stimulation, and there was a good response to painful stimuli. His reflexes were as follows: corneal 2+, light 1+, cough 2+, biceps 3+, knee 3+, ankle 2+, abdominal 0, Babinski 0, ankle clonus 1+ unsustained, plantar withdrawal 3+. The spinal fluid pressure was 180 mm. of Hg, with a cell count of 3 per milliliter. Chest x-ray showed a normal heart shadow, with slight pulmonary congestion and no evidence of effusion. Urinalysis on admission showed a specific gravity of 1.020, pH 5, Sulkowitch 1+, and a rare hyaline cast. The hematocrit

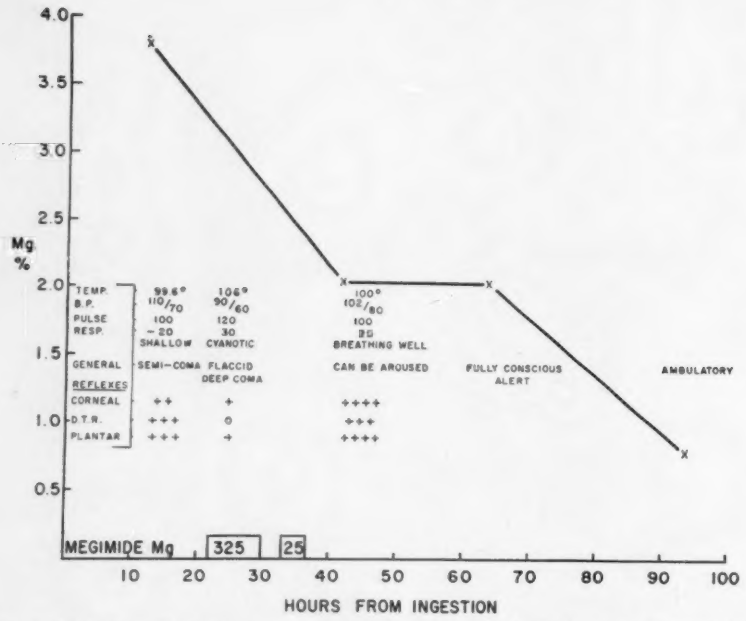

Fig. 3 (Case 5).—Chemical course and blood level of glutethimide in a 47-year-old white man who ingested 12 gm. 12 hours before admission.

was 42, and the sedimentation rate, 13 mm. in one hour. The white cell count was 13,000 with 76% polymorphonuclear cells, 7% band cells, 4% mononuclear cells, and 13% lymphocytes. The icterus index was 7.5, and a total eosinophil count was 72.

Hospital course: Because of the ability to arouse the patient and the satisfactory plantar withdrawal at the initial evaluation, which was 12 hours from the estimated time of ingestion, it was elected to treat the patient conservatively. This was done with gastric lavage, adequate hydration, and repeated neurological examination. The details are presented graphically in Figure 3. Eighteen hours after ingestion, the patient appeared to be in roughly the same clinical state, with no sign of lightening anesthesia. The temperature was 99.8 F, and the blood pressure, 120/90, with a pulse of 100 and respirations 20 per minute, with good thoracic movement. At 24 hours, the neurological examination remained unchanged, but a slight cyanotic tint was noted to the fingernails. Although there was no detectable change in the depth of respirations, the respiratory rate had increased to 28 per minute. At 32 hours, the patient did not appear to be in as good clinical condition. The temperature had spiked rather suddenly to 103 F. The respirations were 38 and considerably more shallow. Oxygen administration was continued, and the blood pressure was 108/70. Deep tendon reflexes were still present but diminished, and the patient was totally unresponsive to any stimuli. At 37 hours, the patient suddenly became more cyanotic, had labored tachypnea, and appeared to be in respiratory distress. The temperature was 102 F; the blood pressure, 90/60; the pulse, 120, and respirations were 30 and shallow. There were diffuse expiratory rhonchi throughout both lungs. Heart sounds were inaudible. Neurological examination was as follows: corneal reflexes 1+; light 1+; biceps 1+; knee 1+; Clonus and Babinski, absent, and plantar withdrawal, 2+. The patient appeared more flaccid. At this point bemegride was started. After 50 mg. there was a sharp increase in respiratory depth and in the patient's color and movement. In 10 minutes, the patient again lapsed into shallow abdominal breathing. Bemegride was continued in small intravenous doses, and when 140 mg. had been injected, there was again excellent stimulation of respiration, with thoracic breathing and generalized increase in tone and responsiveness. In 45 minutes, the patient had lapsed into complete coma and flaccidity, with 1+ corneal, 1+ light, 0 knee, and 0 plantar-withdrawal reflexes and shallow abdominal breathing. A 50 mg. dose (cumulative dose, 240 mg.) produced immediate response, with thoracic respiration and an increase of reflexes to the 2+ level. Regression occurred over a 30-minute period. After a total dose of 325 mg. in six hours, the patient appeared to hold

the respiratory stimulation and required only 25 additional mg. for the remainder of the day to maintain adequate oxygenation. That evening, the patient began breathing heavily and noisily, with marked rhonchi audible in his tracheal tube, and it was felt that he had retention of bronchopulmonary secretions. The thoracic consultant aspirated the patient through the intratracheal tube and extracted about 15 cc. of thick mucopurulent material. After this his breathing was much easier. Tracheotomy was considered but deferred, as the patient showed no further regression in the state of consciousness and no longer required bemegride. At 56 hours, the temperature was 100 F; pulse, 100; blood pressure, 102/80, and the patient had good color and reflexes and deep thoracic respirations. The intratracheal tube was removed at 60 hours from ingestion, and the patient continued to show steady improvement in the degree of consciousness. He was fully awake about 70 hours from the estimated time of ingestion. Renal work-up revealed a chronic pyelonephritis as the basis for his azotemia. He was discharged on the 12th hospital day. Blood concentrations of glutethimide were as follows: 13 hours, 3.8 mg/100 ml.; 42 hours, 2.1 mg.; 64 hours, 2.1 mg.; 104 hours, 0.8 mg.

CASE 6.—A 39-year-old white woman was transferred to our hospital from another city and admitted totally areflexic and in deep coma. She was found unconscious in her bed 60 hours previous to this hospital admission. She had ingested 39 glutethimide tablets, presumably during the night previous to the morning on which she was found. She was admitted in deep coma to another hospital, where she was found to be hypotensive, (blood pressure 80/58) and unresponsive, with absent corneal reflexes. She did have a deep tendon reflex obtainable. She was treated with 7.5 gm. of caffeine and sodium benzoate and 8 gm. of pentylenetetrazol during the next two hours without any change in her clinical appearance. Approximately 24 hours after being found she had active retching and vomiting and aspirated vomitus, with resultant atelectasis of the right middle and right upper lobes. She developed a high fever and was bronchoscoped, with the removal of undigested food from the right middle and right upper bronchi. There was also about a cup of purulent material removed, and the patient was given antibiotics. There was, however, no substantial change in the severe depth of coma, and after 60 hours of observation and conservative treatment it was decided to transfer her to Georgetown University Hospital as a possible candidate for dialysis.

Past history: Patient has been a known diabetic since the age of 19 years and has been controlled with 60 units of isophane (NPH) insulin. At the time of admission to the other hospital, her blood glucose was 207 mg/100 ml. and she had glucose and acetone in her urine. Serum acetone was negative. Fractional urines were collected and she was given multiple injections of regular insulin, and her diabetes was very well controlled throughout her period of coma. At the time of transfer her urine showed only a trace of acetone, and her blood sugar was 216. She is also known to have chronic schizophrenia, with periods of depression and institutionalization. She has been admitted to several mental hospitals in her local metropolitan area and had attempted suicide approximately four to five times previous to the present attempt. Physical examination on transfer to Georgetown University Hospital revealed a 39-year-old well-developed well-nourished white woman in deep coma not responsive to any external stimuli, with a urethral catheter and airway in place. The blood pressure was 106/60; respirations were 40 and shallow. The pupils were dilated to approximately 6 ml. in diameter, with only a barely perceptible response to light. There were no corneal reflexes. Fundi were well visualized without retinopathy. There were coarse rhonchi on late inspiration over the anterior chest bilaterally. The heart rate was 120 and regular, with no murmurs but a ventricular diastolic gallop. There was no clinical edema. A neurological examination revealed total absence of superficial and deep reflexes, absence of plantar withdrawal, and absence of response to deep pain stimuli, such as pinching of the Achilles tendon. The blood sugar was 295 mg/100 ml.; the CO_2 18 per liter, mEq. and plasma acetone was negative. The initial diagnoses were (1) acute glutethimide intoxication; (2) atelectasis, right middle, and lower lobes, with aspiration pneumonia; (3) chronic schizophrenia; (4) diabetes mellitus. The patient was initially titrated with bemegride. The rather poor response to a rather large dose of bemegride suggested that the patient had indeed had a large amount of glutethimide, which should by this time have been absorbed in the gastrointestinal tract. Because of our previous experience and a development of a philosophy expressed later in this paper, we thought that the depth of coma and the dosage of glutethimide warranted a hemodialysis. Dialysis was accordingly begun 65 hours from the time the patient was originally found unconscious. It was carried out for a period of five hours, with use of the right radial artery and the right brachial vein. Patient had average flow rates of 300 ml. per minute, and there was excellent response, with the patient showing some signs of awakening after approximately two and three-quarters hours. This was later followed by a relapse into unresponsiveness except for persistence of the plantar withdrawal reflex. At this point the patient developed beginning coloration of the urine, which was

benzidine-positive and showed some hemolysis in the serial hematocrit tubes. Because of the satisfactory clinical response and the danger of continuing hemolysis, the dialysis was terminated at this point. The patient remained unresponsive through the following day, although a corneal reflex of 2+ intensity could be elicited. Pulse, blood pressures, and respirations remained satisfactory. A plantar-withdrawal reflex persisted. Seventy-eight hours after ingestion, the blood glutethimide level was 1.5 mg/100 cc., although there was a large amount of interfering substance, suggesting the possibility that we were measuring a metabolite. At 83 hours after admission, the patient again began to regress and lost corneal reflexes. Another titration with bemegride was begun, and the patient received that afternoon 1200 mg. of bemegride. After this, she definitely became more reactive and developed deep tendon reflexes and increased plantar-withdrawal, muscle-tone, corneal, and light reflexes. Eighty-seven hours from ingestion, she was very reactive to stimuli and was groaning, moving spontaneously, smacking lips, and coughing and had a slight shuddering reaction resembling an abortive seizure when the gastric tube was removed. At approximately 90 hours from ingestion, the patient awakened fully. The neurological examination became normal. She had smacking motions of her lips and began to talk. The following morning she complained of thirst and hoarseness and had a slight degree of facial edema, good cough reflex, clear chest, and disappearance of the ventricular gallop. She made a good recovery and was discharged on her fourth hospital day. The chest x-ray, which initially showed mottling of both lung fields due to bronchopneumonic infiltration, cleared completely after the cough reflex was restored. Her fever, which reached a peak of 102 F on her second hospital day, had regressed at discharge, and her pulse rate had returned to normal.

Comment

These patients with severe poisoning by a new drug epitomize the almost overwhelming problems besetting the clinical investigator of human toxicology working in the drug decade. The task of obtaining sufficient factual information to manage the poisoned patient rationally is always difficult and often impossible. It is estimated that in the past year, 35,000,000 prescriptions were written for tranquilizing drugs, and a recent index [9] lists 42 products in the seven major categories of chlorpromazine, meprobamate, piperazine, piperidyl, prochlorperazine, promazine, and rauwolfia. If we add hypnotics and sedatives to this list, the number of interrelationships becomes manifold. The present study may serve to illustrate certain generalizations as well as to provide specific information.

Glutethimide has progressed through the classical life pattern of new drugs, which is as follows: enthusiastic introduction—reports of toxicity and overdose, and antidote or management of toxicity. The drug was originally introduced as a "sedative and hypnotic free from undesirable barbiturate effects." [10] It has received wide clinical use as a bed-time sedative, a hypnotic in elderly patients, and an anticonvulsant.[11,12] Nausea and skin rash are reported as side-effects.[10] We have seen one violently pruritic petechial rash in a patient who had never before received the drug or had a clinical allergy. In proportion to its usage, relatively few cases of acute glutethimide intoxication have been reported.[13-15] Several fatal cases are known to the manufacturer.[16] In the present series, deep coma, areflexia, severe hypotension, and hypoventilation occurred with 7 to 12 gm. of glutethimide. Death occurred in a patient to whom it is reasonably certain only 10 gm. was available, but potentiation by alcohol was likely. Cases 1, 2, and 3 were possibly complicated by the synergism of other tranquilizing drugs taken in small amounts. Cases 4 and 5 were probably uncomplicated by other drugs but had secondary infection. We have previously pointed out in relation to barbiturates [17] that the toxicologist dealing with patients must take cognizance of such factors as inaccurate history of dosage, ratio of ingested dose to absorbed dose, time elapsed before treatment, underlying physical state, and individual drug tolerance. It becomes virtually impossible to apply strict statistical methods to human poisonings. There is probably no justification for the prevalent habit of arithmetical juggling used, for example, by Blakey et al.[14] in the translation of an animal LD_{50} into human terms (in this case 88 [0.5 gm. each] of glutethimide).

This becomes manifestly absurd when one considers the fourfold species difference in the glutethimide LD_{50} between the mouse (0.15 gm. per kilogram) and the rat (0.6 gm. per kilogram). When we find one undissolved tablet of glutethimide in the stomach 69 hours after ingestion and lavage, we wonder about the validity of the oral LD_{50} in the first place. The problem of alcohol deserves the serious consideration of any physician prescribing glutethimide in a depressed patient. Alcohol is, after all, the most commonly used "tranquilizing" agent, and many depressed patients nibbling on thoughts of suicide will drink during the deliberations. Since alcohol markedly enhances the solubility of this insoluble drug, it will be difficult to distinguish the effect of rapid absorption from true synergism of cerebral toxicity unless studies are done with use of both agents parenterally.

The cyclic variations in the clinical level of anesthesia noted in these patients are confusing and worthy of comment. Such cycles are much more prominent than in comparable degrees of barbiturate poisoning and can lead to difficulties in evaluating the patient and the effect of treatment. A talking patient may become completely unresponsive in a matter of minutes. It is known that glutethimide is largely excreted in the bile, but it is not certain whether the intestinal resorbate represents inert metabolite or active drug. It is possible that intestinal anaesthesia may slow initial absorption, a mechanism which we have previously noted in severe phenobarbital poisoning.

Bemegride, which was introduced by Shaw, Shulman, and associates,[4-6] has widely been used for sedative intoxications in Europe.[15,18,22] There has been relatively little documentation of clinical poisonings by blood levels and little experience in this country. During the past year, the drug has been under evaluation for acute barbiturate intoxication. Chemical resemblance to glutethimide and the clinical impression of a more rapid response in Cases 1 and 2 led to the present study, which confirms the animal study of Koppanyi,[23] who found that the administration of 4 LD_{50} of bemegride produced a striking response in mice given 1 LD_{50} of glutethimide. Amory[24] noted a marked antagonism in giving 25 mg. per kilogram of body weight of bemegride to rats anesthetized with 100 mg. per kilogram of glutethimide.

We may define the bemegride-glutethimide relationship as a functional antagonism, although the protection does not seem to carry over into very high doses in animals or in man. Bemegride has a probably nonspecific prolonged analeptic effect in other drug poisonings. It stimulates the respiratory and circulatory center and restores reflexes and consciousness. The electroencephalogram improves. However, the drug also produces exaggerated reflexes, muscle twitching, tremor, clonus, hyperventilation, and epileptic potentials in the electroencephalogram. Indeed, bemegride has been employed as an EEG activating agent to replace pentylenetetrazol.[25]

The use of external hemodialysis for the removal of toxic substances from the blood has been the subject of several reports from this laboratory[17,26-28] and will not be reviewed here. Cases 4 and 6 represent a proper use of the artificial kidney in patients with a rapidly deteriorating clinical condition. It is apparent from the change in blood glutethimide levels and recovery in the dialysis bath that glutethimide is dialyzable. Similar experience is available from other laboratories.[29] In retrospect, dialysis was probably indicated in Case 3 and might have prevented this fatality. We were deceived by the apparently light degree of anesthesia in this patient and did not have available at the time a method for the analysis of glutethimide in blood. Alcohol, tranquilizing drugs, and coronary atherosclerosis may have contributed to her death.

On the basis of experience, we can formulate a currently acceptable therapeutic philosophy for acute glutethimide intoxication. Mild cases will have a normal blood pressure and deep tendon reflexes and can be aroused

by painful stimuli. The blood level will probably be in the range of 0.5 to 1.0 mg/100 ml. Such patients can be treated with symptomatic therapy and patience. They will awaken after a period of prolonged sleep. Moderate cases may manifest hypotension, shallow or abdominal breathing, absent or variable deep reflexes, and some plantar withdrawal. Pain response and corneal reflex should be present. The blood level will probably range from 1 to 3 mg/100 ml. Treatment should include early lavage of the stomach, but the physician should desist immediately if apnea or respiratory irregularity occurs. The use of endotracheal suction and oxygen and pressor drugs for hypotension are valuable—care is necessary to avoid overhydration. Cerebral edema represents a major threat. One may titrate the patient with bemegride using 50 mg. increments every 10 to 15 minutes and maintenance doses as needed to keep a "safe" state of anesthesia. It is well to be suspicious if more than 1500 mg. of bemegride is required to lighten anesthesia. The bemegride should be stopped immediately if clonus or convulsions are produced. Severe cases will show hypotension, areflexia, deep coma, absent plantar withdrawal, and pain response. The blood level will probably be above 3.0 mg/100 ml. Such patients should be titrated with bemegride immediately after taking a sample for glutethimide blood level before bemegride is given. Other measures are instituted as one is able. In event of failure to elicit light reflex or plantar withdrawal, a bemegride requirement greater than 1500 mg. on titration, convulsions from bemegride, or later deterioration of clinical state, plans should be made for external hemodialysis on an emergency basis.

Drs. Robert R. Smith, Leo Goldbaum, and Theodore Koppanyi provided helpful suggestions during this work. Gerald Rosenthal and Phyllis Straub gave technical and Rosalie Mancuso, secretarial assistance. Many physicians referred poisoned patients for study.

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The Relationship of Abnormal Vascular Responses to Retinopathy and Nephropathy in Diabetics

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The increasing importance of vascular disease in the diabetic is reflected in recent mortality studies. Whereas in the preinsulin era approximately 18% died of cardiorenal vascular disease, this figure had risen to 54% in 1936 and to as much as 76% in 1955.[1] Furthermore, in juvenile diabetics surviving 25 to 30 years of their disease, 88% have retinopathy (46% retinitis proliferans), 39% have albuminuria, and 44% hypertension.[2]

Only little is known about the etiology and pathogenesis of the vascular disease. It is evident, however, that the more specific lesions, retinopathy and glomerulosclerosis, result from a slowly progressive degeneration of the smaller blood vessels. Retinopathy and glomerulosclerosis are related to various factors, including the duration of diabetes.[3,4]

With use of an ophthalmoscope (magnification $\times 15$), the initial visible change found in the retinopathy of young diabetics is venous congestion (phlebopathy) and small sanguinolent dots (microaneurysms).[5,6] By using the stereoscopic microscope (magnification up to $\times 100$) on the bulbar conjunctiva, one observes in a great number of young diabetics a dilatation of the venules which precedes the retinal venous congestion.[7] The venular dilatation observed in the conjunctiva slowly waxes and wanes and usually remains reversible for at least the first 10 to 15 years of diabetes. Slight perivascular exudation is associated with the venular dilatation, and "hyaline" infiltration, the possible result of prolonged conjunctival exudation, has been correlated to the duration of the disease. Therefore, there appears to be a direct association between the reversible changes and the subsequent degeneration in the vascular bed.[8,9]

It is apparent that the venular dilatation in the conjunctiva is part of an abnormal vasomotor response. It is possible that retinal venous dilatation is evidence of a similarly abnormal vascular response occurring in the small vessels of the retina and that retinopathy (and possible glomerulosclerosis) is produced when the basement membrane of these vessels becomes hyalinized in response to prolonged intermittent exudation.

This investigation represents an attempt to relate, if possible, abnormal vascular responses in the bulbar conjunctiva, both qualitatively and quantitatively, to the retinal and renal complications of young diabetics. The main questions to be answered are (1) do the abnormal vascular responses as reflected in the bulbar conjunctiva appear to a greater degree in diabetics with retinal and kidney disease than in those without these lesions and, (2) do severer vascular responses occur in diabetics showing rapid progression of their vascular disease compared with those showing slow progression?

Material and Method

Sixty unselected hospitalized young diabetics with either retinal or renal complications were chosen for study. They were appproximately evenly divided as to sex, 29 being males and 31,

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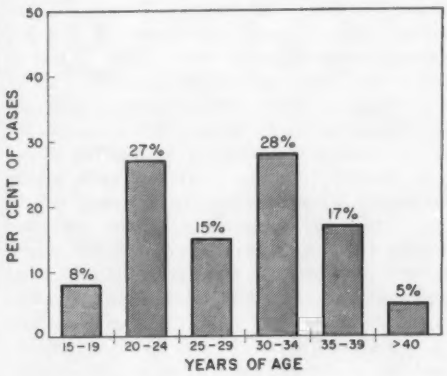


Fig. 1.—Age distribution.

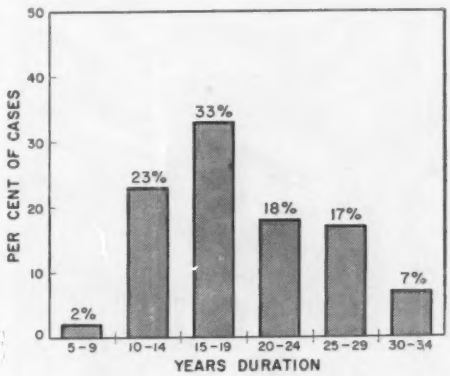


Fig. 2.—Distribution of duration of diabetes.

females. The distribution according to age at the time of examination and duration of diabetes is given in Figures 1 and 2. All but three were under 40 years of age (Fig. 1), and all but one had had diabetes for more than 10 years (Fig. 2). Other than diabetes and its complications, the subjects were free from disease.

After a thorough history and physical examination, each patient was seen by a qualified ophthalmologist. From his report the cases were separated into two groups, namely, those with simple nonproliferative retinopathy and those with retinitis proliferans. Retinitis proliferans was defined as any retinal neovascularization.

Since diabetic glomerulosclerosis is a histologic diagnosis, the term diabetic nephropathy has been chosen. The presence of persistent albuminuria of 50 mg. per 100 ml. of urine or greater, when not obviously due to other causes, was considered presumptive evidence of diabetic nephropathy. Furthermore, the finding of edema and hypertension (defined as persistent elevation of systolic blood pressure over 140 mm. of Hg and diastolic blood pressure over 90 mm. of Hg) were presumptive criteria. Whenever the diagnosis was in doubt, further kidney-function tests were employed, e. g., phenolsulfonphthalein excretion, urea clearance, the nonprotein nitrogen of the blood, and the urinary sediment.

Each case was clinically evaluated for the rate of progression of vascular disease, taking into consideration the duration of diabetes and the extent and severity of the vascular degeneration. By this means the subjects were placed into one of three categories as having had "slow," "moderate," or "rapid" progression. The following criteria were used as the basis for the grouping. If simple retinopathy alone was present after 15 years' duration, if retinitis proliferans alone existed after 20 years, or if combined renal and retinal lesions occurred after 25 years' duration, the case was termed "slow" in progression. If simple retinopathy alone was present between 11 and 15 years' duration, if retinitis proliferans alone existed between 11 and 20 years, or if the combination of retinal and renal

Fig. 3.—Normal vascular pattern.

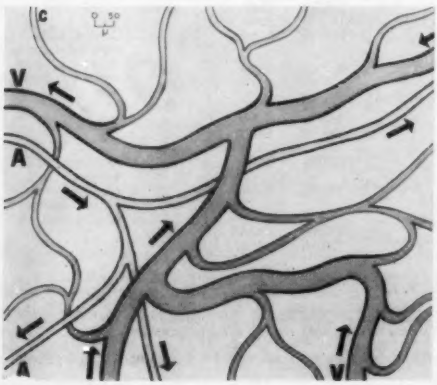


Fig. 4.—Vascular Pattern-Change I.

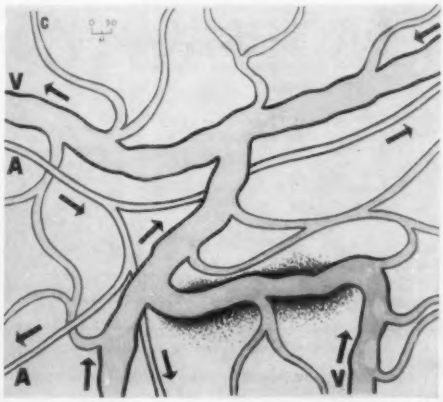


Fig. 5.—Vascular Pattern-Change II.

lesions was present between 15 and 25 years' duration, the rate of progression was termed "moderate." If retinopathy developed before 10 years of diabetes or if retinopathy and nephropathy developed before 15 years' duration, the progression was deemed "rapid." It should be stressed, however, that these criteria were modified by the clinical picture in each case.

The examination of the conjunctival vascular bed was made by one of us (J. D.), independent of the clinical assessment. He knew nothing, therefore, about the history or the result of retinal and kidney studies in the subjects investigated. Three different patterns, designated normal vascular pattern, vascular Pattern-Change I, and vascular Pattern-Change II, could be distinguished in the conjunctival vascular bed of the subjects.[8,9] These pattern changes apparently represented various degrees of vasomotor changes, vascular Pattern-Change II being the severer. Normal vascular pattern (Fig. 3) was characterized by an arteriolar-venular diameter ratio (A/V ratio) of 1:3 to 1:2. Vascular Pattern-Change I (Fig. 4) was characterized by a general distention occasionally associated with fusiform dilatations of the larger venules and localized perivenular edema. The diameters of the arterioles were usually unchanged, occasionally slightly narrowed, and the A/V ratio was consequently variably decreased from 1:4 to 1:8. This pattern change was quantitatively subdivided into three grades. Grade 1 had A/V ratios of 1:5 to 1:4; Grade 2, of 1:7 to 1:6; and Grade 3 had A/V ratios of 1:8 or less. Vascular Pattern-Change II (Fig. 5) was characterized by a general constriction of all vascular elements. Most true capillaries were completely absent, and the tissue, ischemic. The arterioles were markedly constricted, and many were closed. The A/V ratio tended to increase to 1:1. In order to document the conjunctival findings, photographs were taken with a special technique.[10]

The immediate degree of control was assessed by having the 24-hour urinary glucose excretion tabulated for the day of conjunctival examination and for two days prior to this. In addition blood-sugar determinations were made three times during the day of this examination, usually before breakfast and in the late forenoon and late afternoon.

Results

Tables 1, 2, and 3 present the results of the study along with other pertinent data relative to each of the 60 cases.

Eighteen of the entire group of young diabetics exhibited nonproliferating retinop-

TABLE 1.—*Results of Study in Patients with Normal Conjunctival Vascular Pattern*

Case No.	Sex	Age	Duration, Yr.	Retinopathy *		Nephropathy †	B. P.	Prog. of Vasc. Dis.	Cholesterol, Mg./100 Cc.	Other Pertinent Data
				Nonproliferative	Proliferative					
1	F	36	28	Few m. a.; d. v.			110/70	Slow		
19	F	25	16	Few m. a.			150/70	Slow		
46	M	16	12	40–50 m. a.; d. v.; prosthesis of left eye			110/70	Mod.		Central retinal vein thrombosis (o. s.) 2 yr. previous to observation
57	M	18	11	Few m. a.; d. v.			110/75	Mod.	178	
71	F	29	20	30–70 m. a.; d. v.			110/70	Slow		
6	F	24	14		50–70 m. a.; e., d. v.; flat n. v.		120/80	Mod.		
63	F	35	32		Few m. a.; d. v.; many n. v.; a. s.		140/80	Slow	228	No defect in vision
75	F	43	30		30–50 m. a.; d. v.; n. v.; a. s.		140/80	Slow		No defect in vision; ESR; 20 mm./hr.
83	F	21	10		M. a.; n. v.; v. h.		120/90	Rapid	259	
62	F	35	17	Few m. a.; e.		A; L; E; N. P. N. 39 mg./100 cc. Ed.; P. S. P.	170/70	Mod.	247	

* M. a. indicates microaneurysms; d. v., dilated veins; e., exudate; n. v., new-formed vessels; a. s., arteriosclerosis; v. h., vitreous hemorrhage.

† A indicates albuminuria; L, leukocytes >4/microscopic field; E, erythrocytes >4/microscopic field; Ed., clinical edema; P. S. P., phenolsulfonphthalein test <60% in 2 hr.

TABLE 2.—*Results of Study in Patients with Conjunctival Vascular Pattern-Change I*

Case No.	Sex	Age	Duration, Yr.	Pattern Change, Grade	Retinopathy *		Nephropathy †	B. P.	Prog. of Vasc. Dis.	Cholesterol, Mg./100 Cc.	Other Pertinent Data
					Nonproliferative	Proliferative					
7	F	21	17	1	Few m. a.			120/80	Slow	177	
15	M	17	15	1	Few m. a.; d. v.			120/80	Mod.	160	
18	F	32	27	1	5–10 m. a.			125/80	Slow		No retinop. after 25 yr. duration
26	F	16	13	1	Few m. a.			120/75	Slow	250	
27	M	31	11	1	Few m. a.; d. v.			120/80	Mod.		
73	M	35	28	1	M. a.; h.; e.			150/70	Slow	160	
74	F	42	34	1	M. a.; h. e.			140/80	Slow		ESR 25 mm./hr.
14	F	21	16	1		Many m. a.; e.; d. v.; n. v.		120/80	Rapid		
16	F	22	12	1		Extensive r. p.; d. v.		120/90	Rapid		
20	F	33	27	1		Extensive r. p.; d. v.		140/80	Mod.	312	Slow progression 1948–1955
44	M	24	16	1		Severe r. p.; d. v.		120/80	Rapid		Totally blind 1 yr. after (1956)
65	M	32	15	1		Mod. r. p.; e.; d. v.; a. s.		120/80	Mod.	222	
87	M	28	26	1		Severe r. p.; d. v.; e.		120/80	Mod.		Hypophysectomy 1957
58	M	24	15	1		Early r. p.; 50 m. a.; e.	A; L; E; N. P. N. 36 mg./100 cc. P. S. P.	120/80	Mod.	400	Had m. a. 1953
2	F	32	23	1		Early r. p.; d. v.; e.	A; L; E; N. P. N. 90 mg./100 cc.; P. S. P.	140/100	Mod.		
47	F	33	26	1		Mod. r. p.; d. v.	A; L; P. S. P.	130/100	Mod.		
56	M	23	12	1	Many m. a.; d. v.		A; L; P. S. P.	150/100	Rapid		Coma 3 times 1944–1950
70	M	31	16	1		Extensive r. p.	A; L; E; Ed.; P. S. P.	190/110	Rapid	294	
77	F	31	11	1		Severe r. p.	A; L; E; N. P. N. 37 mg./100 cc.; P. S. P.	180/100	Rapid		
78	M	34	20	1		Mod. r. p.; E; d. v.; a. s.	A; L; E; N. P. N. 60 mg./100 cc.; P. S. P.	180/100	Rapid		0 coma, ESR 60 mm./hr.
4	M	25	14	2	Few m. a.; d. v.; venous sacculations		A; E	120/80	Mod.	675	Necrobiosis lipoidica
8	M	24	22	2	Few m. a.			125/80	Slow		
9	M	27	15	2	10–20 m. a.; h.			130/80	Mod.		
45	M	31	18	2	Few m. a.; d. v.			120/80	Mod.		
59	M	21	15	2	4–5 m. a.			130/85	Slow	197	
68	F	22	14	2	Few m. a.			110/80	Slow	260	Coma 12 times
23	F	28	16	2		Extensive r. p.		120/80	Rapid		
25	M	31	16	2		Extensive r. p.		120/70	Rapid	264	Hypophysectomy 1955 with little or no improvement
28	M	32	15	2		Extensive r. p.; d. v.; e.		130/90	Rapid	254	
66	M	28	18	2		Mod. r. p.; e.; d. v.	A; L; E; U. Cl. 69 %; N. P. N. 35 mg./100 cc.	130/60	Rapid	186	
84	M	30	19	2		Severe r. p.; E; d. v.	A; L; E; P. S. P.	130/80	Rapid	320	ESR 80 mm./hr.
13	F	19	15	2		M. a.; d. v.; few n. v.	A; L; E; N. P. N. 30 mg./100 cc.	140/90	Rapid	181	
82	M	34	20	2		Extensive r. p.; d. v.; h., e.	A; L; E; N. P. N. 88 mg./100 cc.	180/100	Rapid	416	
64	M	37	21	3	50 m. a.; d. v.; E.; a. s.			120/70	Mod.	287	
17	F	23	12	3		Many m. a.; h.; n. v.		105/65	Rapid	138	Developed glaucoma 1 yr. after (1956)
3	M	24	20	3		50 m. a.; h.; e.; d. v.; a. s.	A; E; P. S. P.	140/95	Mod.	237	
10	F	20	5	3		Numerous h.; e.; d. v.; n. v.	A; L; E; N. P. N. 42 mg./100 cc.; P. S. P.	170/110	Rapid	507	Necrobiosis, lipoidica
81	M	32	20	3		Numerous h.; e.; v. h.; n. v.	A; L; E; P. S. P.	180/100	Rapid	313	ESR 48 mm./hr.

* M. a. indicates microaneurysms; d. v., dilated veins; h., hemorrhages; e., exudate; n. v., new-formed vessels; r. p., retinitis proliferans; a. s., arteriosclerosis; E., edema (retinal).

† A indicates albuminuria; L, leukocytes >4/microscopic field; E, erythrocytes >4/microscopic field; P. S. P., phenolsulfonphthalein test <60% in 2 hr.; Ed., clinical edema; U. Cl., urea clearance.

TABLE 3.—*Results of Study in Patients with Conjunctival Vascular Pattern-Change II*

Case No.	Sex	Age	Duration, Yr.	Retinopathy *		Nephropathy †	B. P.	Prog. of Vasc. Dis.	Cholesterol, Mg./100 Cc.	Other Pertinent Data
				Nonproliferative	Proliferative					
48	M	34	29		Severe r. p.		140/90	Mod.		Blind 1 yr. later (1956)
86	F	39	23		Numerous m. a.; e.; v. h.; v.		110/75	Mod.	255	ESR 14 mm./hr.
69	F	48	29		Extensive r. p.; loss of vision right eye	A; L; E; N. P. N. 48 mg./100 cc.	160/80	Mod.		
29	F	35	23		Extensive r. p.; d. v.	A; L; E; P. S. P.	170/80	Rapid		
60	F	37	27		Extensive r. p.; d. v.; h.; e.; a. s.	A; N. P. N. 27 mg./100 cc.; P. S. P.	130/80	Mod.		
72	M	38	21		h.; e.; prothesis o. s.	A; L; E; N. P. N. 66 mg./100 cc.	170/85	Rapid	338	
11	F	22	19		Numerous h.; e.; n. v.; d. v.	A; E; L; P. S. P.; N. P. N. 43 mg./100 cc.	140/105	Rapid		
43	M	27	26		Early r. p.; e.; d. v.	A; P. S. P.	160/94	Mod.	158	
55	F	21	10		Severe r. p.	A; E; L; P. S. P.; Ed.	210/150	Rapid		Died 1 yr. after observation diabetic glomerulosclerosis
76	F	32	17		Preretinal h.; severe r. p.; d. v.; a. s.	A; L; P. S. P.; N. P. N. 45 mg./100 cc.	180/110	Rapid		ESR 52 mm./hr.
79	F	28	14		Mod. r. p.; h.	A; E; L; P. S. P.	155/95	Rapid		ESR 41 mm./hr.
80	M	37	31		Extensive r. p.; many obliterated veins	A; E; L; P. S. P. N. P. N. 35 mg./100 cc.	180/95	Mod.	240	ESR 32 mm./hr.

* R. p. indicates retinitis proliferans; m. a., microaneurysms; e., exudate; v. h., vitreous hemorrhage; n. v., new-formed vessels; d. v., dilated veins; h., hemorrhages; a. s., arteriosclerosis.
† A indicates albuminuria; L, leukocytes >4/microscopic field; E, erythrocytes >4/microscopic field; P. S. P., phenolsulfonphthalein test <60% in 2 hr.; Ed., clinical edema.

athy alone; sixteen had proliferating retinopathy alone, and twenty-six had a combination of retinopathy and nephropathy. Fifteen cases had hypertension, all of whom also had nephropathy. It was of interest to note that in such a series of unselected young diabetics with vascular complications, none had nephropathy without also demonstrating retinopathy, and of the 26 cases with nephropathy, all but 3 had retinopathy of the proliferating type.

Abnormal vascular responses in young diabetics with retinopathy and nephropathy contrasted to young diabetics without such lesions: From Tables 1, 2, and 3 it will be seen that of the 60 diabetics, 10 exhibited normal vascular patterns (17%), 38 showed vascular Pattern-Change I (63%), and 12 showed vascular Pattern-Change II (20%). Thus as many as 83% of the young diabetics with vascular disease showed abnormal conjunctival vascular patterns. In Table 4 this finding is compared with similar data obtained from 69 juvenile diabetics without vascular disease and from 70 healthy nondiabetic controls.[8] It will be noted that the young diabetics with retinopathy and nephropathy showed abnormal vascular patterns significantly more frequently and severely than those young diabetics without retinal and kidney lesions ($\chi^2=15.28$; $P<0.01$; $N=1$).

Relationship of conjunctival patterns to the degree of vascular disease: Table 5 correlates the conjunctival patterns to the degree of vascular disease, the data being collected from Tables 1, 2, and 3. It will be seen that in general the young diabetics who had normal vascular pattern demon-

TABLE 4.—*Abnormal Vascular Responses in Young Diabetics With Retinopathy and Nephropathy Contrasted to Young Diabetics Without Such Lesions and Healthy Nondiabetic Subjects*

	60 Young Diabetics With Vascular Disease, %	69 Juvenile Diabetics Without Vascular Disease, %	70 Healthy Nondiabetic Controls, %
Normal vascular pattern	17	49	99
Vascular Pattern-Change I	63	48	1
Vascular Pattern-Change II	20 (83)	3 (51)	0 (1)

TABLE 5.—*Relationship Between Conjunctival Vascular Patterns and Retinopathy and Nephropathy*

	Conjunctival Vascular Patterns		
	Normal Vascular Pattern	Vascular Pattern-Change I	Vascular Pattern-Change II
Simple retinopathy alone	5	13	0
Proliferative retinopathy alone	4	10	2
Retinopathy and nephropathy	1	15	10

TABLE 6.—*Relationship Between Conjunctival Vascular Patterns and Rate of Progression of Retinopathy and Nephropathy*

	Conjunctival Vascular Patterns		
Rate of Progression of Vascular Disease	Normal Vascular Pattern	Vascular Pattern-Change I	Vascular Pattern-Change II
Slow	5	8	0
Moderate	4	13	6
Rapid	1	17	6

strated but little vascular disease. Nine out of the ten showed only slight to moderate retinopathy. None demonstrated hypertension, and only one (Case 62) had signs of nephropathy. In contrast to this, all of the 12 diabetics who had severe conjunctival vascular response—vascular Pattern-Change II —demonstrated severe vascular disease. Ten of the twelve diabetics had advanced nephropathy (83%), and all of them severe retinitis proliferans. Half of the cases showed hypertension. In general, the 38 diabetics who exhibited the more frequent vascular Pattern-Change I showed vascular disease to less degree than those diabetics with vascular Pattern-Change II but to a greater degree than those demonstrating normal vascular pattern. Thus 13 had simple retinopathy alone (34%); 10, retinitis proliferans alone (27%), and 15 had nephropathy (39%). The diabetics showing the most marked degree of venular distention (Grade 3) in general demonstrated more extensive vascular disease than those showing less venular distention (Grade 1 and 2) of vascular Pattern-Change I. This relationship between the conjunctival pattern abnormality and the extent of vascular disease was statistically significant. (The x^2 test applying Yate's correction equaled 7.84, $N=1$; $P<0.01$.)

Relationship of conjunctival patterns to the rate of progression of vascular disease: Since the development of retinopathy and nephropathy is related to the duration of diabetes, the finding of a correlation between the conjunctival pattern abnormality and the extent of vascular disease might be explained by a similar positive relationship between the severity of conjunctival vascular patterns and duration of diabetes in this particular series. That this is not the fact can be seen from Tables 1, 2, and 3. Not only is the average duration of diabetes in three groups approximately the same (normal vascular pattern, 19.0 years; vascular Pattern-Change I, 17.8 years; and vascular

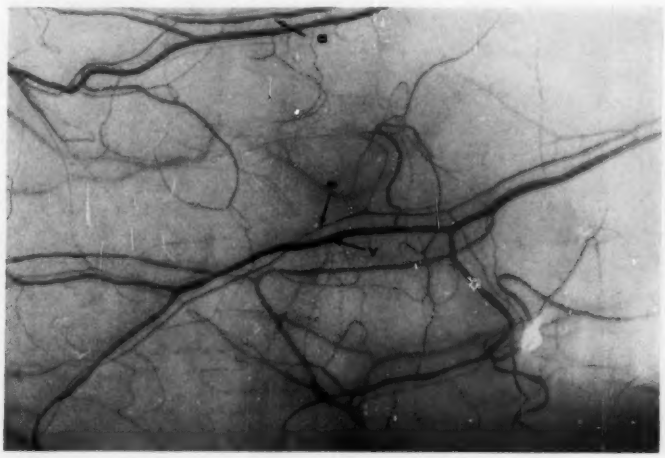


Fig. 6.—The conjunctival vascular bed of a diabetic woman (Case 75, age 43 years; duration of diabetes, 30 years) showing normal vascular pattern (arteriolar (*a*)-venular (*v*) diameter ratio 1:2) and slow progression of diabetic vascular disease; reduced 38% from mag. ×48.

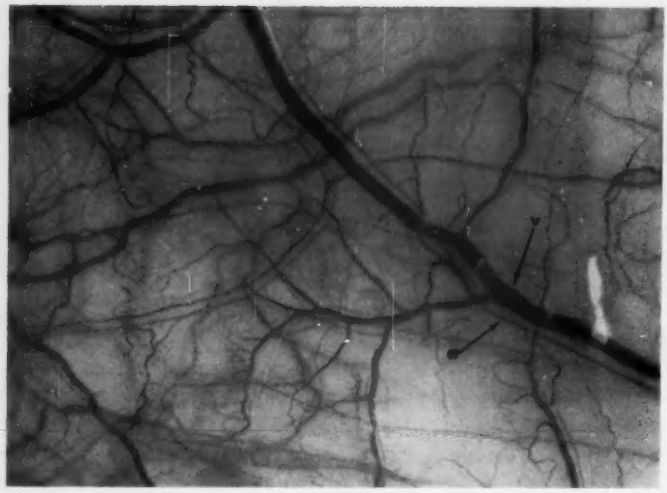


Fig. 7.—The conjunctival vascular bed of a diabetic man (Case 64, age 37 years; duration of diabetes, 21 years) showing vascular Pattern-Change I (arteriolar (*a*) -venular (*v*) diameter ratio 1:7) and moderate progression of diabetic vascular disease; reduced 34% from mag. ×48.

Pattern-Change II, 22.4 years), but the distribution of the durations is also nearly the same. Therefore the three groups of diabetics are comparable with regard to duration of diabetes. Furthermore, analysis of blood sugars and urinary glucose excretions also demonstrated that the groups were comparable as far as the immediate degree of control of diabetes. Table 6 demonstrates the relationship between the conjunctival patterns and the rate of progression of retinopathy and nephropathy. It will be seen that in general the diabetics who exhibited normal vascular pattern (Fig. 6) are the diabetics who had the best prognosis with respect to rate of development of their vascular disease (note in Table 1, Cases 1, 63, and 75, with minimal retinopathy despite more than 28 years' duration of their disease). In contrast, the young diabetics demonstrating vascular Pattern-Change II (Fig. 8) have a much severer prognosis with moderate or rapid progression of their vascular disease (note in Table 3, Case 55, with severe nephropathy, who, despite only 10 years' duration, died due to diabetic glomerulosclerosis one year after the observation; Cases 76 and 79, who had severe retinopathy and nephropathy after 14 and 17 years' duration of diabetes). The cases

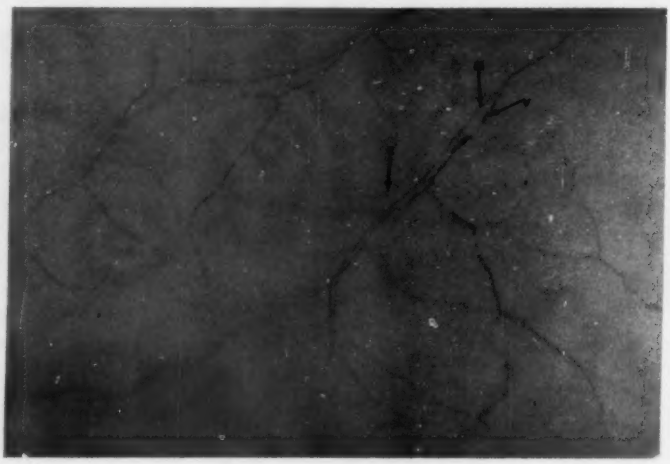


Fig. 8.—The conjunctival vascular bed of a diabetic woman (Case 76, age 32 years; duration of diabetes, 17 years) showing vascular Pattern-Change II (arteriolar (*a*)-venular (*v*) diameter ratio 1:1) and rapid progression of diabetic vascular disease; reduced 38% from mag. ×48.

who exhibited vascular Pattern-Change I (Fig. 7) in general showed rates of progression of their vascular disease between those showing normal vascular patterns and vascular Pattern-Change II. The cases who had the severest venular distention (Grade 3) generally demonstrated a poorer prognosis than those with less venular distention. (Note Case 10, who had severe retinopathy, nephropathy, and hypertension after only 5 years' duration.)

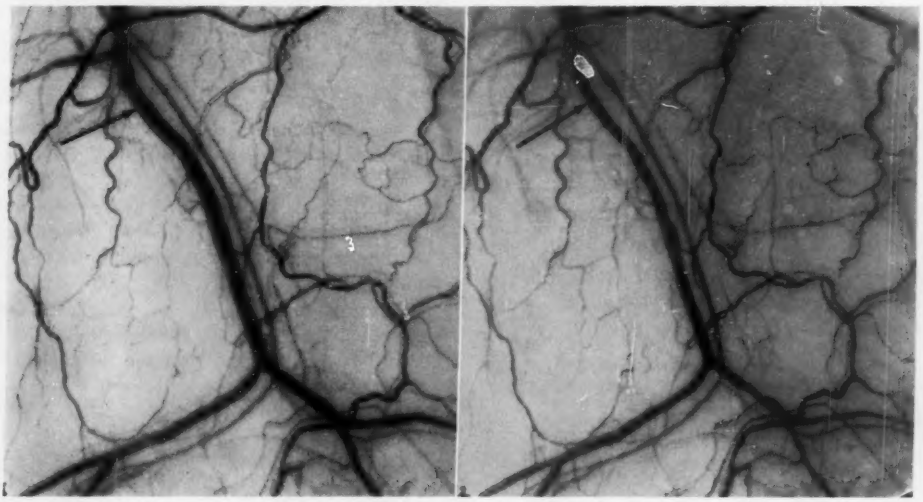
Comment

The significant relationship between the degree of small vessel degeneration in the retina and the kidney and the vascular response patterns observed microscopically in the bulbar conjunctiva of young diabetics is of considerable interest. This association cannot be explained by differences in duration of diabetes or various degrees of immediate control, because these factors are comparable in the groups studied. Since the well-defined pattern deviations may be reversible and are present even in patients with diabetes of short duration, the changes in the pattern are not caused by vascular degeneration. Thus the relationship indicates that the abnormal response patterns of the smaller blood vessels are an important factor in the development of diabetic retinopathy and possible nephropathy.

Even though a positive relationship is present between abnormal vascular patterns and the degree of retinopathy and nephropathy, this relationship does not always hold true for the individual case. The explanation for this discrepancy may lie in the fact that the response patterns of the vessels may slowly reverse or progress. However, in our experience with young, long-term diabetics these fluctuations are small, and those showing vascular Pattern-Change II have never been observed to reverse. Such a shift from the normal vascular pattern to vascular Pattern-Change I in one patient was seen in Case 27 and is demonstrated in Figure 9.

Ophthalmoscopic evidence of abnormal response patterns in the retina is the presence of venous congestion which is observable particularly in young diabetics, even prior to the development of microaneurysms.[5,6] Owing to the small magnification (× 15), it is not possible to observe small blood vessels of similar sizes to those observable

Fig. 9.—The conjunctival vascular bed of a diabetic man (Case 27, age 31 years; duration of diabetes, 11 years) showing initially vascular Pattern-Change I. At reexamination two months later (careful treatment), the venular dilatation and the previously observed perivascular edema had disappeared (normal vascular pattern); reduced 27% from mag. × 48.



in the bulbar conjunctiva. Thus the nature of the abnormal vasomotor response changes in the retina cannot be clearly defined with the techniques available today.

The contention that the abnormal vasomotor response is a precursor in the development of diabetic retinopathy is not unlikely when it is considered that other types of retinopathy, e. g., the hypertensive, the toxemic, and that of the newborn infant (retrolental fibroplasia) all are initiated and produced by abnormal vasomotor changes in the small vessels. In these latter three conditions, the relationship between abnormal functional alterations and retinopathy is clearly understood. The retinal changes develop rapidly because the arteriolar side of the vascular bed, which is of paramount importance for the nutrition of the retinal tissue, is affected. This is in contrast with the condition in diabetes, where it takes approximately 10 to 15 years' duration of the disease to develop retinopathy, most likely because the functionally less important smaller blood vessels, the venules, are particularly involved. Even though abnormal vasomotor changes in the small retinal vessels appear important in the development of diabetic retinopathy, no doubt many other factors play a role.

Summary

A study of vascular response patterns observed microscopically in the bulbar conjunctiva was made in 60 young diabetics with retinopathy and nephropathy.

A significant relationship was found between the conjunctival-pattern abnormality and the extent of small blood vessel degeneration irrespective of duration of diabetes.

This suggests that abnormal vasomotor changes in the small retinal vessels play an important role in the development of diabetic retinopathy.

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Addendum

Since completion of this paper, an interesting work by Sigroth has appeared which indirectly supports the concept of this paper, that abnormal functional changes are related to subsequent degeneration in the smaller blood vessels of diabetics. (Sigroth, K.: Reflex vasodilatation of the fingers in the study of peripheral vascular disorders, with special reference to diabetes mellitus, Acta med. scandinav. [Supp. 325] 157: 1, 1957.)

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Chronic Uremia Due to Polycystic Renal Disease Treated with the Artificial Kidney

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Since the clinical use of an artificial kidney was described by Kolff and Berk,[1] in 1944, various types of dialyzers have been applied in the treatment of renal failure. A prefabricated, presterilized, disposable coil kidney * is now commercially available. Through its simplicity of preparation and operation,[2] we use it not only in the emergency of acute uremia but also in the treatment of the patient having chronic renal disease.

During the past five years (1952 to 1957), 13 patients with polycystic renal disease have been seen by the artificial kidney team of the Cleveland Clinic Hospital. Eight patients were severely ill and were treated with dialysis. They received a total of 14 dialyses. Two patients received three dialyses each. All of these patients, of course, received the necessary medical management.

Five patients were treated conservatively only, without dialysis.

The purpose of this paper is to review our experience with hemodialysis in patients with severe uremia due to polycystic renal disease and to determine whether or not and under what conditions dialysis is effective in the management of this slowly progressive disease.

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From the Division of Research, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute; Fellow in the Division of Research, The Cleveland Clinic Foundation (Dr. Nakamoto).

* Manufactured by Baxter Laboratories, Morton Grove, Ill.

Artificial Kidneys Used

The disposable coil kidney was used for seven patients, and the Skeggs, Leonards, and Heisler dialyzer,[3] for one patient. Both dialyzers employ ultrafiltration as well as dialysis. These artificial kidneys perform three functions: (1) removal from the blood of retention products such as urea, creatinine, uric acid, sulfates, phosphates, and unknown metabolites; (2) correction of electrolyte imbalance through equilibration with the constituents of the rinsing fluid, and (3) removal of water (with the electrolytes) through ultrafiltration, thus reducing edema when necessary.

Clinical Features

Patients Treated with Dialysis.—Seven of the eight patients treated with dialysis knew that they had had polycystic renal disease from 3 to 19 years; in one patient the diagnosis was made on admission.

Signs and Symptoms (Tables 1 and 2).—Nausea and vomiting were present immediately before admission in all eight patients. Moderate arterial hypertension was present in seven patients, average, 170/110 (150-200/90-120). Other signs, symptoms, and complications were cramping pain in the legs, temporary hematuria, headaches, pericarditis, uremic twitching, dehydration, temporary urinary infection, pulmonary congestion, abdominal distention, and uncontrolled diarrhea.

Six of the eight patients were under good medical management prior to admission. All eight patients were severely ill, and most appeared to be in the terminal phase of uremia.

TABLE 1.—*Incidence of Clinical Symptoms and Signs in Dialyzed Patients and in Patients Treated Conservatively*

	Patients, No.	Average Age, Yr.	F. H.*	Duration of Known Polycystic Renal Disease, Yr.	Nausea, Vomiting	Severe Diarrhea	Cramping Pain in Legs	Extremely Distended Abdomen	Temporary Urinary-Tract Infection	Temporary Hematuria
Dialyzed	8	49 (31–67)	3	(7 pts.) 3–18	8 3, severe 5, mild	1	3	2	2, E. coli 1, P. aeruginosa	5
Not dialyzed	5	42 (35–59)	2	(5 pts.) 3–19	2, mild	0	2	0	1, Bacillus faecalis	3

* Family history of polycystic renal disease.

TABLE 2.—*Incidence of Clinical Symptoms and Signs*

	Patients, No.	Uremic Twitching	Marked Dehydration	Convulsion	Headache	Duration of Arterial Hypertension, Yr.	Pericarditis	Pulmonary Congestion	Medical Management Before Admission
Dialyzed	8	3	3	0	4	(7 pts.) 3–12	2	2	6 well 2 poor
Not dialyzed	5	0	0	0	5	(5 pts.) 2–17	0	1	4 well 1 poor

Patients Not Treated with Dialysis.—In the five patients not dialyzed, uremic symptoms were milder (Tables 1 and 2). Nausea and vomiting occasionally occurred in two patients. There was no evidence of pericarditis, diarrhea, distended abdomen, uremic twitching, or dehydration. None of the five patients seemed to be in a serious, critical, or terminal phase when admitted. However, they were hypertensive. The systolic pressure ranged from 150 to 210, and the diastolic pressure, from 95 to 135 mm. of Hg.

Blood Studies in the Eight Patients Treated with Dialysis (Table 3).—At the time of admission blood urea values ranged from 181 to 368 (average, 263) mg. per 100 ml. The alkali reserve ranged from 9.1 to 19.7 (average, 12.7) mEq. per liter. In three patients serum sodium values were less than 125 mEq. per liter, and in two patients serum potassium values were greater than 6.0 mEq. per liter.

Blood Studies in the Five Patients Not Treated with Dialysis (Table 3).—At the time of admission, blood urea ranged from 33 to 113 (average, 75) mg. per 100 ml., and alkali reserve, from 21.0 to 23.5 (average, 21.7) mEq. per liter. There were no other electrolyte imbalances upon admission.

TABLE 3.—*Blood Data Before and After Dialysis and on Discharge in Eight Patients*

Patient No.	Dialysis	Urea, Mg./100 Ml.		HCO_3^-, mEq./L.		Uric Acid, Mg./100 Ml.		Urea, Mg./100 Ml.	HCO_3^-, mEq./L.	Uric Acid, Mg./100 Ml.
		Before	After	Before	After	Before	After			
1D	(1)	315	135	14.6	21.0	16.8	12.1	72	26.5	5.2
	(2)	222	90	19.3	23.1	12.0	6.5			
	(3)	168	108	16.3	18.0	11.3	5.3			
2D		219	102	19.7	24.4			102	20.6	
3D	(1)	312	105	12.5	21.8	10.4	3.5	108	25.2	
	(2)	234	89	17.6	25.2	11.5	3.8			
4D		201	87	12.1	19.3	12.6	4.4	134	20.1	
5D	(1)	297	81	10.8	20.1			174	20.6	
	(2)	400	135	13.3	21.4					
6D	(1)	348	81	8.2	20.6			165	19.3	
	(2)	342	90	16.8	23.1					
	(3)	372	87	14.6	23.1					
7D		181	72	9.1	18.1	11.8		90		
		216	96	13.3	21.8	7.8	3.6			
Average		273	97	14.2	21.5	11.8	5.6	121	22.1	

Results

Eight Patients Treated with Dialysis.—Seven patients showed chemical and clinical improvement after dialysis (Table 3) and left the hospital much improved. Four of the seven patients are still alive and doing well for three months to one year since dialysis. Two were able to return to their previous occupations. Two (61 and 69 years old) do not work but enjoy a reasonable amount of activity. Three patients died in two weeks to two months after discharge from the hospital. One patient died in the hospital from a far-advanced polycystic renal disease after 35 days of treatment, despite three dialyses. Four patients had recurrent hematuria that abated within two days; the one patient who died had continuous gross hematuria. Seven patients were able to keep a high-caloric diet after treatment. Protein was restricted to 50 gm., but salt was allowed. Sodium lactate (20 to 80 mEq. per day) was given by mouth, when indicated by low alkali reserve. The one patient who died in the hospital was unable to maintain a high-caloric diet, partially due to intestinal obstruction. Temporary urinary tract infection was present in two patients: Escherichia coli in one and Pseudomonas aeruginosa in the other. Both were successfully treated with antibiotics. The severe diarrhea in one patient ceased after dialysis. Two patients developed a low-sodium syndrome which was characterized by malaise, nausea, and vomiting and was corrected by intravenous administration of sodium chloride.

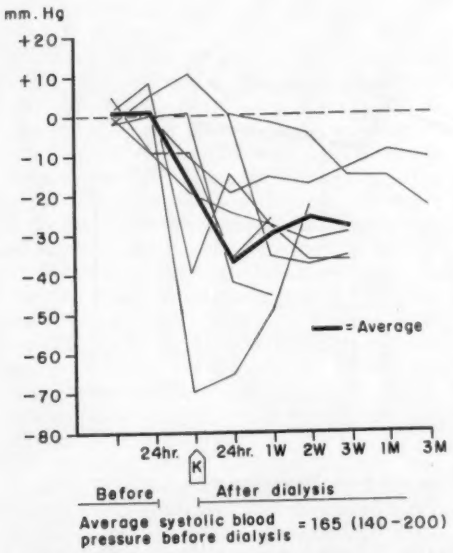

Fig. 1.—After dialysis there was a change in systolic pressure in each of eight patients, as indicated by the thin lines. The average systolic pressure before dialysis was 165 (140-200). The average decrease was 30 mm. of Hg (heavy line). The patient with normal blood pressure (140) showed the least decrease.

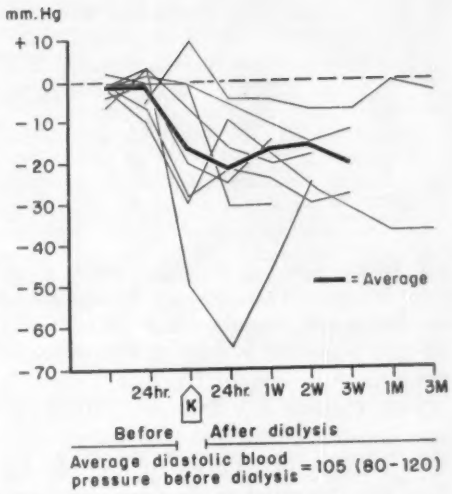

Fig. 2.—Average diastolic blood pressure in eight patients was 105 (80-120). The average decrease (heavy line) after dialysis was 20 mm. of Hg.

Dialysis reduced the blood urea from an average of 263 to 97 mg. per 100 ml. (Table 3). Alkali reserve was raised from an average of 12.7 to 21.1 mEq. per liter. Serum uric acid was lowered from an average of 11.7 to 5.5 mg. per 100 ml. These chemical improvements were maintained at almost the same levels until the time of discharge, an average of 16 days later.

In reviewing the data it was a surprise to find that after dialysis arterial blood pressures decreased significantly. Although seven patients had known hypertension for a period of 3 to 12 years before dialysis, the blood pressure became normal after dialysis

TABLE 4.—*Blood Data in Five Patients Treated Conservatively*

Patient No.	Date of Admission	Upon Admission			After Treatment		
		Urea, Mg./100 Ml.	HCO_3^-, mEq./L.	Uric Acid, Mg./100 Ml.	Date of Follow-Up	Urea, Mg./100 Ml.	HCO_3^-, mEq./L.
1C	Jan., 1952	108	21.4	6.2	Sept., 1956	72	15.1
2C	April, 1952	60	21.0	8.2	Oct., 1956	78	20.1
3C	Dec., 1952	33	23.5	6.0	July, 1956	36	
4C	May, 1955	60	21.0	6.0	Jan., 1957	87	26.1
5C	Dec., 1952	113	21.4		June, 1957	153	21.8
Average		75	21.7	6.6		85	20.8

and remained so for at least 3 weeks in all eight patients. There was an average fall in systolic blood pressure of 30 mm. of Hg (Fig. 1) and an average fall in diastolic pressure of 20 mm. of Hg (Fig. 2).

Five Patients Not Dialyzed.—Hypertension persisted during and after management until the time of writing. All five patients have since returned to their previous occupations. There were no significant changes in blood chemistry (Table 4) before or after conservative treatment and at a later control date. One patient developed a cerebral vascular accident in 1952 but recovered satisfactorily. One patient showed evidence of a low serum sodium value two months ago, which was corrected.

Case Report of Patient Treated with Dialysis

PATIENT 7D (Fig. 3 and Table 3).—A 43-year-old man was admitted for emergency treatment because of renal failure. During the previous six months he had tired easily and had lost 20 lb. in weight. For two weeks prior to admission he had frequent attacks of nausea and vomiting, and for the last week, gross hematuria. There was no diarrhea, cramping pain of lower extremities, or headache. The blood pressure was 135 systolic and 80 diastolic. There was no known hypertension at any time. There was no family history of

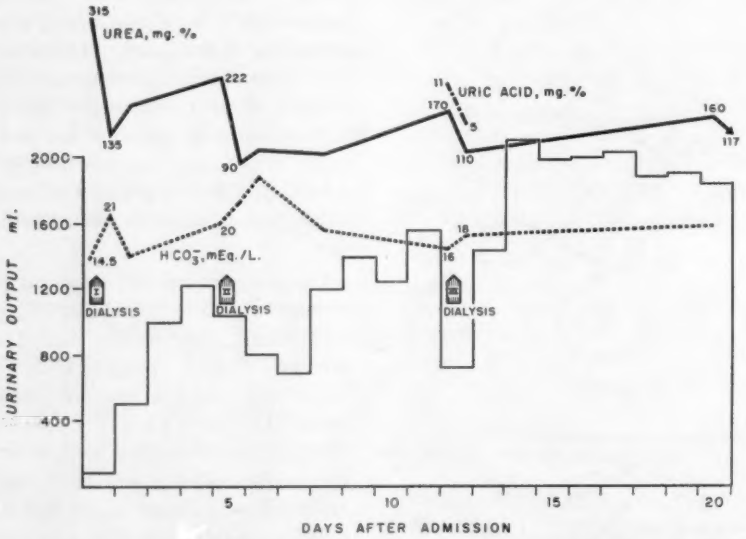

Fig. 3.—A 45-year-old man with large polycystic kidneys and severe uremia complicated by pericarditis. He was treated with dialysis three times. The blood urea was reduced by each dialysis from 315-135 mg. per 100 ml. The uric acid was also reduced as indicated for the third dialysis from 11-5 mg. per 100 ml. The alkali reserve (HCO_3^-) increased each dialysis (14.5 to 21 mEq. per liter, etc.), owing to removing of acid metabolites and addition of $NaHCO_3$ from the rinsing fluid to the blood.

The urinary output (lower part of the graph) increased to over 2000 ml. per day after the third dialysis. Patient has been doing well for more than six months after treatment.

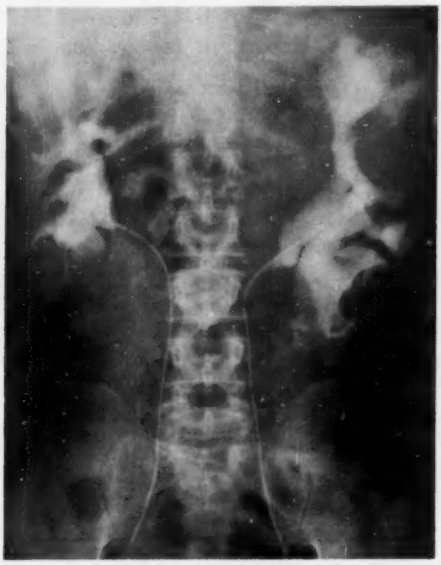

Fig. 4.—First the clinical condition of the patient was improved by treatment with the artificial kidney. Then diagnostic studies became feasible. Retrograde pyelography revealed this typical picture of large polycystic kidneys.

polycystic renal disease. Kussmaul's respiration and uremic breath odor were present. The skin was pale; there were no petechiae. The dryness of oral mucosa and injection of the pharynx were noted. There was no engorgement of the cervical veins. The heart was normal in size; the sounds were of fair quality, and the rhythm was regular. A "to-and-fro" friction rub was heard along the sternal border but no thrill, murmur, or gallop rhythm. The abdomen was markedly distended; the bowel sounds diminished, and the enlarged nodular nontender kidneys were palpable on both sides. Uremic twitching, hyperactive tendon reflexes and Babinski's sign were present. Peripheral edema was minimal. Urinalysis disclosed gross hematuria but no sugar. The specific gravity was 1002. Hemoglobin was 13.1 gm. per 100 ml., and hematocrit reading was 42 ml. per 100 ml. Serum electrolyte values were as follows: sodium 140, potassium 3.7, chloride 96, and alkaline reserve 14.6 mEq. per liter. Blood urea was 315 mg., and creatinine, 7.8 mg. per 100 ml. Uric acid in serum was 16.9 mg. per 100 ml. The electrocardiogram was interpreted as being consistent with acute pericarditis.

The diagnosis was renal failure due to polycystic renal disease. The patient was dialyzed on the 2d, the 6th, and the 13th hospital days (Fig. 3). During the first dialysis blood urea decreased from 315 to 135 mg. per 100 ml., and serum uric acid, from 16.8 to 12.1 mg. per 100 ml. (Table 3). The unbalanced electrolytes were corrected. There was immediate symptomatic improvement after the first dialysis.

The diagnosis of polycystic renal disease was confirmed by retrograde pyelogram (Fig. 4). A high-caloric, low-protein diet was started, and daily urinary output increased to 1200 ml. on the 5th day and to 2000 ml. on the 15th day. On the day of discharge, 35 days after admission, blood urea was 72 mg. per 100 ml. Pericardial friction rub persisted until discharge from the hospital. He was discharged with a high-caloric diet containing not more than 50 gm. of protein per day. He was instructed to take enough fluid to maintain a urinary output of at least 1500 ml. daily. Sodium lactate was prescribed, 20 mEq. three times daily with meals.

Since discharge from the hospital, he has been well and working full time. Pericardial friction rub has disappeared.

Comment

In chronic uremia a single six-hour dialysis may break the spell of continuous vomiting and misery and may be as effective as six weeks of difficult frustrating medical management. Whereas the results of medical management are doubtful, a temporary improvement of the uremia by dialysis is almost a certainty. It is impossible to predict how long such improvement will last; if renal function does not recover it will not exceed a week. In severe cases, one dialysis may not be enough and subsequent dialyses may be necessary to consolidate the initial improvement. Polycystic renal disease progresses so slowly that dialysis appears justified.

In the present eight patients with severe or apparently terminal uremia due to polycystic renal disease, four have been restored to several months to one year of useful life.

A decrease in arterial systolic and diastolic blood pressure after dialysis was found in all patients who previously had been hypertensive. Whether or not this decrease occurs consistently or whether we have just been very lucky, we cannot decide on the basis of our experience to date. As we have obtained no fall in blood pressure in other forms of chronic renal failure, the reduction here

obtained should not make us overoptimistic. A favorable result probably will not be obtained when the hypertension of polycystic renal disease has become malignant.

The survival time of the patients with severe uremia, although improved by dialysis, is shorter than that of patients with less uremia that needed no dialysis.

Summary and Conclusion

Eight patients with severe uremia due to polycystic renal disease were treated with the artificial kidney. Seven patients were discharged much improved after an average of 16 hospital days. Four are living and doing well. Two others have resumed their previous occupations, and two, aged 61 and 69 years, returned home to a quiet existence. Three patients were improved on discharge but died from recurrent hemorrhage or other complications two to eight weeks later. In one patient improvement lasted only a few days, and he died in the hospital 35 days after admission.

Most of the eight patients here described probably were beyond recovery with the medical management alone. In others dialysis shortened the period of hospitalization. In serious cases more than one dialysis was necessary to consolidate the initial improvement. It sometimes takes more than 14 days for renal function to recover. Hemorrhage from cysts need be no contraindication for dialysis. Surprisingly, following dialysis hypertension decreased an average of 30 mm. of Hg systolic and 20 mm. of Hg diastolic and remained low for at least three weeks. Fortunate as this was, it is unexplained and needs confirmation on a larger number of patients with polycystic renal disease and hypertension.

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Radioactive Cyanocobalamin (Vitamin B_{12}) in Renal Disease

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Since 1952, Co^{60} cyanocobalamin (vitamin B_{12}) has been used to confirm the diagnosis of pernicious anemia. Its main advantage is that it is an effective diagnostic agent whether or not cyanocobalamin or liver extract has been taken as a form of treatment. It is in this particular group of patients who have been given treatment and in whom the ordinary diagnostic laboratory tests have been obscured by the effects of the therapy that this test is particularly useful.

Four methods for measuring the absorption of orally administered radioactive cyanocobalamin are currently used. After the oral administration of Co^{60} cyanocobalamin, measurement of radioactivity in the stool,[1] hepatic uptake of Co^{60} cyanocobalamin,[2,3] and recovery of the radioactive cyanocobalamin in the urine[4] have all been used. Recently Co^{56} cyanocobalamin has been measured in the plasma after oral administration.[5] Schilling's method of measuring Co^{60} cyanocobalamin in a 24-hour urine sample has been widely adopted because of its simplicity and because of the fact that it reflects accurately the amount of cyanocobalamin absorbed from the gastrointestinal tract. However, because this test depends not only upon absorptive factors of the intestinal tract but also upon renal mechanisms for excretion, certain limitations exist. It has been our experience that patients with renal insufficiency while absorbing Co^{60} cyanocobalamin adequately are unable to excrete it in the time period allotted for the usual test. In these instances, therefore, the routine measurement of the 24-hour urine excretion gives values similar to those found in patients with pernicious anemia. It is the purpose of this report, therefore, to point out some of these limiting factors as well as to relate our experience with this test as a possible assay method for intrinsic factor.

Submitted for publication Aug. 5, 1957.

From the Radioisotope Service and Medical Service, Veterans' Administration Hospital.

Methods

A total of 39 patients were studied, 13 of whom were proven to have pernicious anemia. Twelve patients with varying types of renal disease and renal insufficiency were observed, as well as fourteen patients with miscellaneous diseases. The method of Schilling was used, which consists essentially of oral administration of 0.5μc. of Co^{60} in the form of cyanocobalamin in aqueous solution (diluted to 30 cc. with water). Breakfast was allowed one hour later. Two hours after the oral Co^{60} cyanocobalamin, 1000μg. of nonradioactive cyanocobalamin was given intramuscularly as a flushing dose. Urine was collected for a 24-hour period, and a 96-hour fecal collection was done in some instances. The percentage recovery of radioactivity in the urine sample was measured by comparing a 1500 cc. aliquot with a standard made up of 0.5μc. of Co^{60} cyanocobalamin in 1500 cc. of water. The fecal specimen was diluted and counted in a similar manner. The hepatic uptake studies were carried out according to the method of Glass, wherein multiple uptake measurements were made over the skin projection of the liver six to eight days after ingestion of the 0.5μc. oral dose of Co^{60} cyanocobalamin and compared with measurements made on normals.

When assaying intrinsic-factor preparations the same general plan was followed. Patients with proven pernicious anemia were given 0.5μc. of Co^{60} cyanocobalamin orally, followed by 1000μg. of cyanocobalamin intramuscularly two hours later. Urine and fecal collections for 24 and 96 hours, respectively, were made. The same procedure was then repeated, combining the administration of the intrinsic factor preparation with the oral Co^{60} cyanocobalamin. The increased recovery from the urine when an intrinsic-factor

TABLE 1.—*Urinary Excretion of Co^{60} Cyanocobalamin in Patients with Pernicious Anemia*

Patient	24-Hr Urine Recovery, %
H. J.	0.03
P. B.	0.60
C. L.	0.82
F. H.	1.80
A. A. N.	1.00
A. M. N.	1.50
F. M.	3.90
D. S.	1.40
J. D.	0.00
G. G.	1.60
J. C. H.	0.00
P. McB.	0.12
W. K.	2.30

preparation was administered is an index of the efficacy of the material.

Results

The Schilling test was performed on 13 patients with proven pernicious anemia (Table 1). The 24-hour urine recovery of Co^{60} cyanocobalamin ranged between 0 and 3.9%, with only two values being over 2% of the administered dose. This would correlate well with previous studies. In two of the patients 96-hour fecal measurements were performed and were found to be 52% and 98%, respectively. This represents a far greater percentage than would normally be found in the stool. Several of these patients were used to assay various intrinsic-factor preparations. Many of these extracts resulted in no increase in the urinary excretion of radioactive cyanocobalamin. When a preparation was found to be potent by this method it was then used to treat a patient with pernicious anemia in relapse. The Figure represents the reticulocyte responses obtained in two patients with pernicious anemia in relapse treated with oral cyanocobalamin and an intrinsic-factor preparation previously proven to be potent by the test described.

Eleven patients with known renal disease and varying degrees of renal failure were studied with the Schilling test. As noted in Table 2, in each patient with a moderate to marked elevation of the BUN there is a corresponding low 24-hour urine recovery of cyanocobalamin. On the other hand in those patients with a relatively normal BUN the 24-hour urine recovery is correspondingly closer to normal. In Patient E. K., suffering from congenital polycystic kidneys and a perirenal abscess, the 24-hour urine recovery of cyanocobalamin was 3% at a time when the BUN was 26 mg/100 cc.

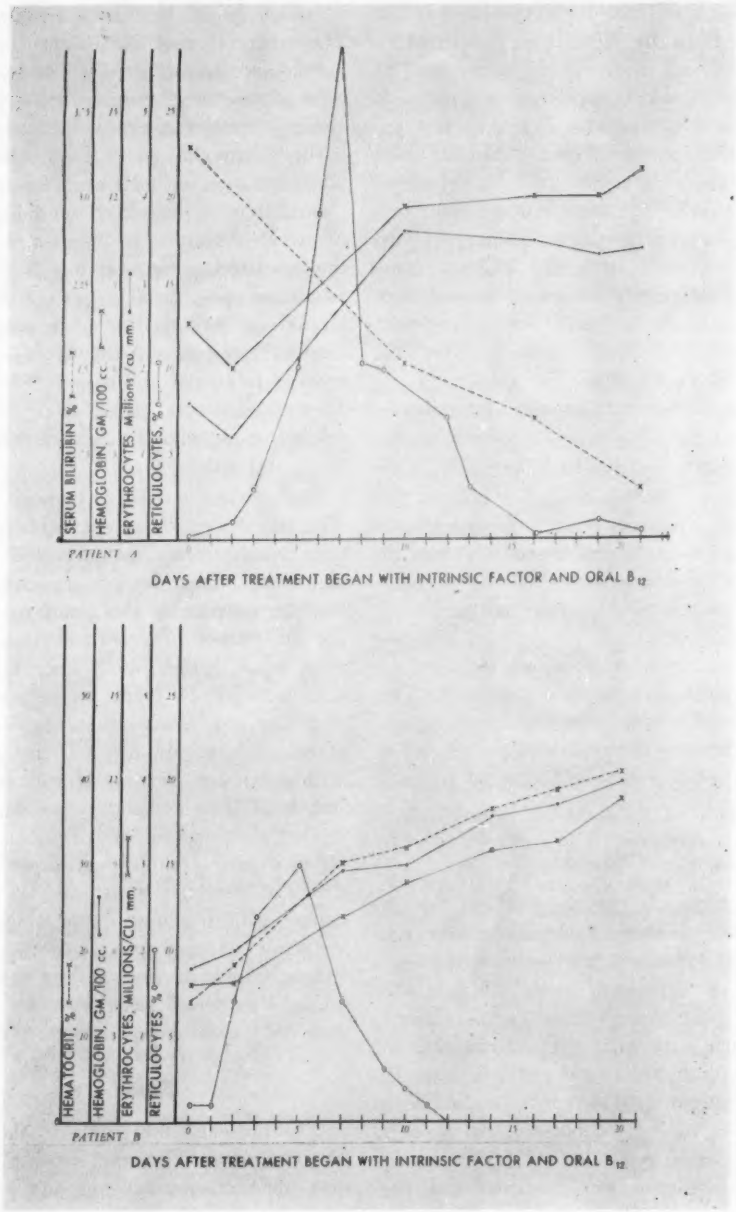
TABLE 2.—*Urinary Excretion of Co^{60} Cyanocobalamin in Renal Disease*

Patient	Diagnosis	BUN, Mg./100 Cc.	24-Hr. Urine Recovery, %	Remarks
E. V.	Arteriolar nephrosclerosis	25	14.5	HBP, ASHD, BPH
A. K.	Arteriolar nephrosclerosis	70	2.0	Creatinine 8.6; anemia secondary to renal disease; HBP, ASHD
E. K.	Congenital polycystic kidneys	26 11	3.0 11.0	Before & after drainage of perirenal abscess
G. A.	Diabetic glomerulosclerosis	74	2.7	Chronic pyelonephritis
R. S.	Chronic glomerulonephritis	19	22.0	
W. T.	Chronic pyelonephritis	42	2.5	PSP 4.5 in 15 min.
R. M.	Diabetic glomerulosclerosis	30	4.3	Renal biopsy
R. J.	Arteriolar nephrosclerosis	65	4.2	Creatinine 6.8
H. S.	Glomerulonephritis	72	4.1	Creatinine 9.5
L. K.	Benign prostatic hypertrophy	35	13.0	
J. A.	Urinary tract	111.5	0.6	
H. H.	Bilateral hydronephritis, pyelonephritis, & prostatic hypertrophy	190	3.4	

TABLE 3.—*Urinary Excretion of Co^{60} Cyanocobalamin in Miscellaneous Diseases*

Patient	Diagnosis	24-Hr. Urine Recovery, %	Remarks
A. D.	Lymphosarcoma of stomach	3.8	Deep x-ray to stomach
I. Z.	Hodgkin's disease	12.7	
J. P.	Total gastrectomy	1.0	(Benign gastric ulcer) hypochromic anemia
M. P.	Alcoholism and malnutrition	12.4	
F. B.	Anemia, c. u.*	34.6	
W. B.	Cardiac decompensation	6.2	Hypertensive arteriosclerotic heart disease
C. B.	Marie-Strumpell	12.7	
D. M.	Steatorrhea	9.4	Chronic pancreatitis
F. S.	Avitaminosis, malnutrition diarrhea	3.8	
S. S.	Pellagra	8.0	
S. C.	Total gastric resection	11.0	Ca of stomach
E. M.	Total gastric resection	2.0	
L. C.	Malnutrition, alcoholism	13.4	
Mrs. T.	Combined degeneration of cord	5.6	

* Etiology unknown.



After drainage of the perirenal abscess and a lowering of the BUN to 11, the 24-hour urine recovery was 11%. Many of the 24-hour urine determinations fell well within the diagnostic range corresponding to that of pernicious anemia. If the renal status had not been known in these patients, an erroneous diagnosis might have been suggested.

Fourteen patients with miscellaneous diseases (Table 3) were studied with the Schilling test. Following total gastrectomy in three patients, two showed 1% and 2%,

respectively, and one had 11% recovery in 24 hours from the urine. One patient had a lymphosarcoma involving the entire wall of the stomach, which was treated with deep x-ray therapy, and the Schilling test revealed 3.8% recovery from the 24-hour urine sample. Another patient with a combined degeneration of the cord without other evidence to suggest pernicious anemia revealed a 5.6% recovery from the 24-hour urine sample. One elderly patient with avitaminosis, malnutrition, and a chronic severe diarrhea showed a 3.8% recovery from the 24-hour urine sample. The remaining patients were essentially within normal limits.

The Schilling test potentially is an excellent method of assaying intrinsic-factor preparations. In this study we utilized this procedure in patients with pernicious anemia and total gastrectomies to select potent intrinsic-factor preparations. These preparations were then used on untreated pernicious anemia patients, and, as seen in the two patients who were treated, a good reticulocyte response was obtained (Figure). This response is in agreement with Schilling and others who have demonstrated the efficacy of this test as a means of assaying intrinsic factor.

Comment

This study confirms the value of the urinary excretion method of radioactive cyanocobalamin in patients with pernicious anemia and is in agreement with other studies showing poor absorption of cyanocobalamin in patients with total gastrectomy and the malabsorption syndrome. Heinle was the first investigator to demonstrate failure of absorption of cyanocobalamin by showing increased fecal excretion of Co^{60} cyanocobalamin in the stools of patients with pernicious anemia after oral administration. Schilling subsequently described a simpler clinical approach by measuring urinary excretion of orally administered Co^{60} cyanocobalamin. The demonstration of little or no radioactivity in the urine has been used to indicate the defect of absorption of cyanocobalamin in pernicious anemia patients. Poor absorption of Co^{60}-labeled cyanocobalamin has also been shown to occur after total gastrectomy,[6-13] intestinal strictures associated with megaloblastic anemia,[14] and sprue.[15] In the latter two instances the administration of intrinsic factor has been shown to have no effect on the absorption of cyanocobalamin. In the case of strictures the impaired absorption has been ascribed to abnormal bacterial growth, and administration of tetracycline (Achromycin) and chlortetracycline (Aureomycin) has increased intestinal absorption. In sprue the absorption defect exists along with those related to fat, vitamin A, carbohydrate, calcium, and iron.

All of these studies have been concerned with the absorption of cyanocobalamin, with little emphasis on the effect of the renal status as related to urinary excretion. It was the purpose of this study to emphasize the importance of a normal renal function. As previously described, when the urine is collected for 24 hours in performing the Schilling test, abnormal values often correspond with the low levels found in patients with pernicious anemia. However, when the length of time of urinary collection is extended, a normal amount of radioactivity can be recovered from the specimen. No evidence of defective absorption of the radioactive cyanocobalamin exists, since the fecal excretion of radioactive material is in the range found in normal persons and the urinary excretion over a longer period of time falls in the normal range.

Summary

The present study confirms the value of the Co^{60} cyanocobalamin urinary excretion test for pernicious anemia and compares it with the methods involving measurement of radioactivity in the stool and hepatic uptake of Co^{60} cyanocobalamin (vitamin B_{12}). It is in agreement with other studies showing poor absorption of cyanocobalamin in patients with total gastrectomy and the malabsorption syndrome.

The feasibility of using the Schilling test as a method of assaying various preparations containing intrinsic factor is also confirmed. It must be emphasized, however, that the use of intrinsic factor with oral cyanocobalamin can be considered only as an experimental tool at this time and that routine administration of these preparations is not to be encouraged.

The limitations imposed on the urinary excretion test by renal disease are pointed out, but it must be emphasized that they need not detract from the usefulness of the test. The present study merely stresses the importance of considering the renal status in interpreting the results of the test.

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X-Ray Manifestations of Peptic Ulceration During Corticosteroid Therapy of Rheumatoid Arthritis

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Peptic ulcers have been known to occur in the human race for many decades and indeed are not unknown in animals, such as dogs, cows, sheep, and, rarely, rats.[4] Furthermore, correlations have been shown between the incidence of peptic ulcers and such things as population density and severe stress. It has been said that between 5% and 10% of our population can expect to have an ulcer at some point during their lifetime. The occurrence of such ulcers has come to be associated with a certain clinical syndrome of abdominal pain relieved by food and antacids, abdominal tenderness, and definite radiographic abnormalities which are demonstrable in most cases.

The advent in 1949 of the use of cortisone and corticotropin (ACTH) in the treatment of rheumatic disease [5] and more recently of synthetic analogues, such as prednisone and prednisolone,[3] began an era of a new sort of peptic ulcer—one which tends to be associated with minimal (in some cases none) symptoms and which may present an altered radiographic and fluoroscopic appearance. The incidence of such corticosteroid-induced, or activated, ulcers has been shown to be 26% in a series of 68 rheumatoid arthritis patients treated with corticotropin, cortisone, or hydrocortisone.[6]

The present paper was stimulated by experiences encountered in the roentgen study of a series of rheumatoid arthritis patients treated with prednisone. In all, 49 such patients have been observed at the Clinical Center of the National Institutes of Health, and a total of 12 (24%) have developed peptic ulcers while receiving therapy. The occurrence of a fatal hemorrhage in two of these patients, one from a duodenal ulcer and the other, a gastric, led to a review of all radiographic examinations of the gastrointestinal tract performed upon these patients. This study revealed certain radiological information which we believe should be brought to the attention of physicians concerned with the diagnosis and treatment of patients given corticosteroid therapy.

The roentgen diagnosis of peptic ulceration is dependent upon certain established criteria, the most important of which is the demonstration of an ulcer crater. Other ancillary findings of considerable value include the formation of an incisura, pylorospasm, tenderness, and adjacent inflammatory changes, with edema, radiating mucosal folds, and a spastic, irritable, and/or deformed duodenal bulb. The demonstration of an ulcer crater in the stomach may be expected in a higher percentage of cases than in duodenal ulcers. In fact, it has been stated [2] that skilled radiologists utilizing compression and air-contrast spot films associated with careful fluoroscopy may demonstrate an ulcer crater in 80% to 90% of patients with active gastric lesions. The detection of ulcer craters in the duodenum is more difficult. Most authors report crater demonstration in less than 50% of the patients examined, perhaps explained by the fact that the duodenum is relatively thin, the ulcer craters are shallower, and there is

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Fig. 1 (Case 1).—Stomach filled with barium, demonstrating prepyloric ulcer along lesser curvature associated with a deformed duodenal bulb.

less opportunity for muscle contraction and mucosal edema.

Our experience indicates that valuable indirect manifestations of ulceration, such as reflex motor disturbances, tenderness, and edema, may be completely lacking in patients with active ulceration while receiving corticosteroid therapy, as will be evident from the case reports to follow. The lack of ancillary findings of ulceration in these patients should not deter the radiologist from establishing a diagnosis but rather should serve as a challenge. Every skill and technique must be used to demonstrate the presence of an ulcer crater. The fluoroscopic findings may be entirely normal, but compression films, air-contrast studies, and large films in various projections may reveal the presence of a small crater nonvisible under fluoroscopic conditions.

Report of Cases

CASE 1.—A 31-year-old white woman was admitted to the Clinical Center on March 12, 1957, with a history of rheumatoid arthritis of five months' duration. The process originated in the knees and gradually spread to involve the hands, wrists, ankles, feet, and elbows. At the age of 16, a diagnosis of duodenal ulcer was established. A gastrointestinal examination performed in November, 1956, demonstrated an old deformed duodenal bulb but no evidence of active ulceration. Previous medication consisted of corticotropin and prednisone.

Positive findings in physical examination were those of swelling, tenderness, and pain on motion of the hands, feet, ankles, knees, and right elbow. Subcutaneous nodules were palpable near the left olecranon process. Laboratory studies revealed a

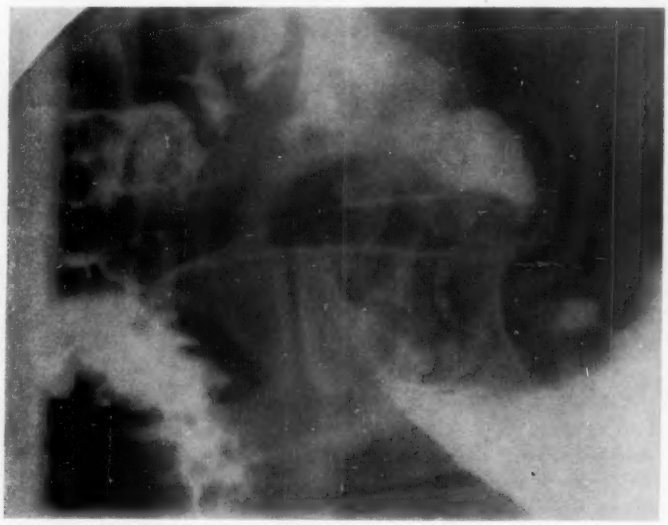


Fig. 2 (Case 1).—Enlarged compression spot film of antrum, showing ulcer crater.

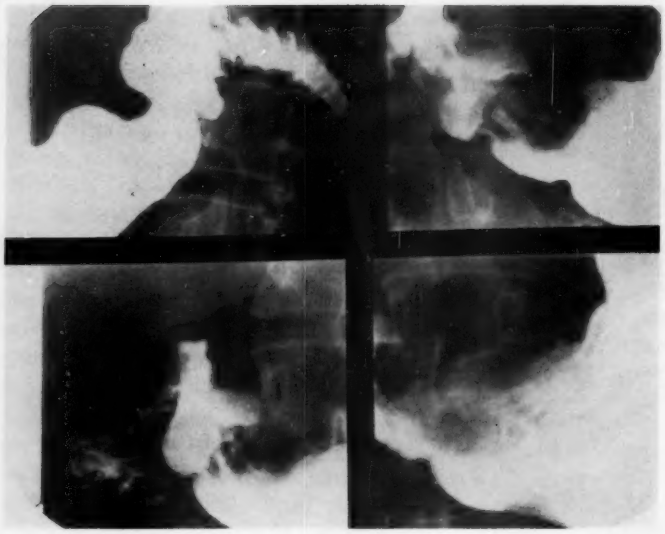


Fig. 3 (Case 1).—Series of spot films demonstrating disappearance of ulcer crater.

sheep-cell agglutination titer of 512, a hematocrit of 36%, sedimentation rate (Westergren) of 85 mm. in one hour, C-reactive protein of 4+, and a reversal of the albumin-globulin ratio. A gastrointestinal series on March 20, 1957, demonstrated the presence of a gastric ulcer as well as a deformed duodenal bulb (Figs. 1 and 2).

Comment.—This patient was not receiving prednisone at the time the gastric ulcer was discovered. Because the patient developed excessive anxiety, the medication had been gradually reduced, starting on Feb. 28, 1957, with final discontinuation immediately prior to the gastrointestinal examination. The lack of definitive abdominal symptoms was an important feature in this case. After the x-ray study of the stomach, the patient was carefully questioned and acknowledged occasional epigastric pain. The characteristic symptom-complex of pain with relief by alkali or the intake of food was completely lacking. Likewise, at fluoroscopic examination, the patient denied tenderness on palpation over the ulcer crater, although radiographically there was some associated spasm. The roentgen findings, however, were characteristic of a gastric ulcer, and the lesion responded well to medication with healing of the crater, as demonstrated by subsequent study (Fig. 3).

CASE 2.—A Negro woman, aged 32, was admitted to the Clinical Center on July 7, 1953, with a history of rheumatoid arthritis of three years' duration. The first joint involved was the right knee, with subsequent affliction of both wrists, hands, elbows, knees, and ankles. Past therapy included gold injections, cortisone, salicylates, and quinacrine (Atabrine).

Physical examination on admission revealed tenderness and swelling, with pain on motion of the joints mentioned above. Both wrists were ankylosed. Laboratory studies were negative except for a sedimentation rate (Westergren) of 118 mm. in one hour, a hematocrit of 28%, and a reversal of the albumin-globulin ratio (2.5:6.4). The white blood cell count was 3500. X-rays of the joints

Fig. 4 (Case 2).—Note shallow ulcer crater with deformed duodenal bulb. Previous examination showed entirely negative findings.

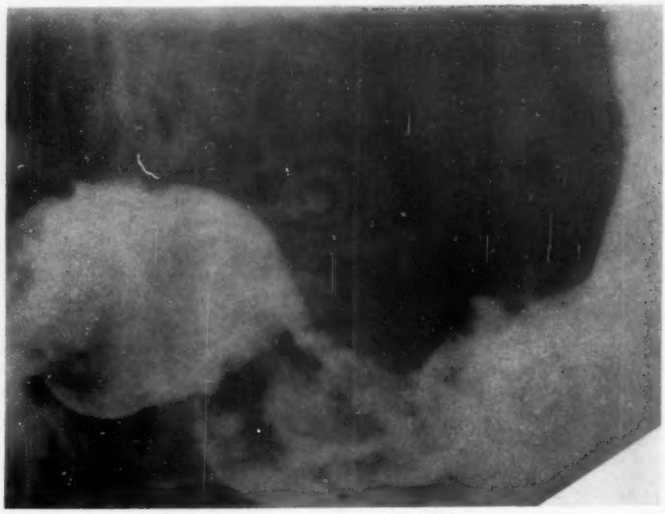


Fig. 5 (Case 2).—Ulcer crater no longer present. Duodenal bulb shows very little deformity.

showed extensive destruction of articular cartilage and adjacent bony structures. A gastrointestinal study on Dec. 6, 1954, was normal.

Prednisone therapy, 30 mg. daily, was initiated on Dec. 17, 1954, with marked relief of the articular complaints. Although the patient was without gastric symptoms, a repeat gastrointestinal examination on Jan. 6, 1955 (Fig. 4), demonstrated a shallow duodenal ulcer with an associated deformity of the duodenal bulb. One week later, the patient complained of epigastric pain and shortly thereafter became depressed. An antiulcer regimen was instituted, and the duodenal ulcer healed, as demonstrated by subsequent x-ray studies (Fig. 5), but a severe psychosis developed necessitating hospitalization in a mental institution.

Comment.—This patient was of interest for several reasons. First, a shallow ulcer crater with associated duodenal deformity was demonstrated while the patient was still without abdominal symptoms. Fortunately, a gastrointestinal series had been performed prior to administration of prednisone; hence, it was known that the duodenal bulb was not deformed prior to the therapy. Such a base-line study is important, since a deformed bulb may exist prior to the use of corticosteroid therapy and could lead to an erroneous diagnosis of active duodenal ulceration.

This patient also presented a second complication of this type of therapy, namely, a severe psychosis. Howell and Ragan [6] observed depression in 14 of 68 patients receiving corticosteroid therapy. One of their patients developed a severe psychosis. Levin [7] likewise stressed the psychotic complications of corticosteroid medication. As of the time of writing of this paper, the patient is still hospitalized in a mental institution. The gastrointestinal symptoms have been alleviated by ulcer medication.

Case 3.—A 42-year-old white woman was admitted to the Clinical Center on April 19, 1954, with a history of rheumatoid arthritis of 13 years' duration. Prior to admission, the patient had received salicylates, gold therapy, corticotropin, and cortisone. The corticotropin was discontinued after six months, owing to untoward effects. Cortisone was started in January, 1951, and continued until time of admission. The patient sustained multiple rib fractures and a compression fracture of T-8 during this therapy.

Physical examination on admission revealed joint involvement of the hands, wrists, knees, and feet. Bilateral choroiditis, severest on the left, was noted on examination of the eyes. Laboratory work included a sedimentation rate (Westergren) of 22 mm. in one hour, hematocrit of 43.5%, and a sheep-cell agglutination titer of 128. X-rays demonstrated soft-tissue swelling, osteoporosis, and destruction of the cartilage and bone at the articular surfaces. X-rays of the spine demonstrated a fracture of T-8, with roentgen evidence of old healed rib fractures.

On Nov. 17, 1954, the cortisone was discontinued and prednisone was started in dosages of 30 mg. daily, resulting in improvement sufficient to allow

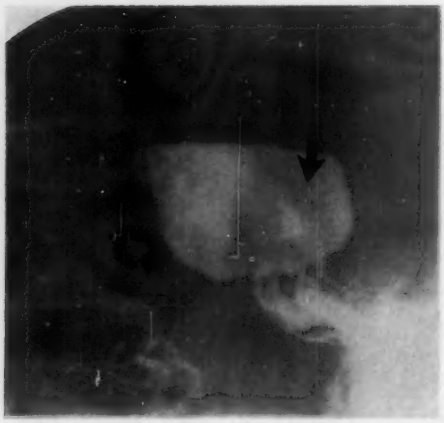


Fig. 6 (Case 3).—Ulcer crater in duodenal bulb, revealing surrounding radiolucent halo due to edema.

the patient to return to work. In May, 1955, a new compression fracture of T-5 was demonstrated. Epigastric pain was first experienced during the summer of 1955, and on Aug. 12, 1955, a gastrointestinal examination demonstrated a typical duodenal ulcer (Fig. 6) with an edematous ring surrounding the ulcer crater. Treatment consisting of belladonna tincture, phenobarbital, and aluminum hydroxide gel resulted in rapid healing of the ulcer crater, in spite of continuation of prednisone at dosage levels of 17.5 mg. daily. A repeat x-ray study of the stomach and duodenum revealed healing of the ulcer, with minimal residual deformity.

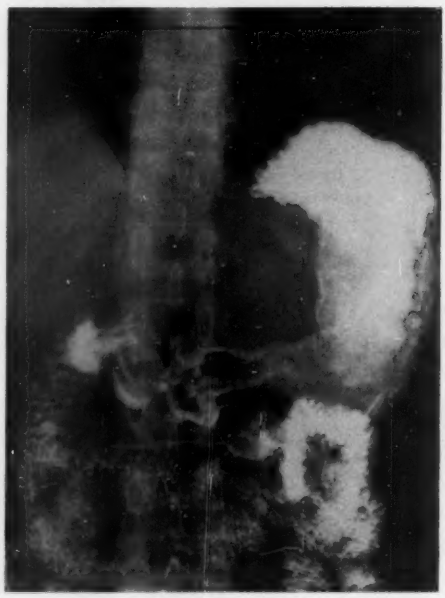
Comment.—This patient experienced another of the complications of such steroid therapy, namely, osteoporosis with multiple fractures, a development which in some patients forces discontinuation of the steroid. She exhibited a characteristic ulcer crater surrounded by a zone of edema, with very little indication of localized irritability. The patient denied the presence of tenderness on direct palpation over the lesion. The ulcer, in this case, healed during continued corticosteroid therapy. Such patients must be under close and continued observation, as hemorrhage or perforation may develop rapidly, often without warning, as illustrated by Case 5.

Case 4.—A 44-year-old white woman was seen in the admissions and follow-up department of the Clinical Center on March 21, 1957, with a history of rheumatoid arthritis of nine years' duration. Six months prior to the onset of arthritis, she developed psoriatic lesions of the fingernails. The first episode of arthritis started in her knees and, shortly thereafter, spread to involve both feet, hands, shoulders, and elbows. The patient received typhoid fever vaccine, salicylates, and, finally cortisone, in 1951, the latter enabling the patient to return to work. The initial daily dose of 300 mg. of cortisone was gradually tapered to a 25 to 50 mg. daily maintenance dose. In March, 1955, the cortisone was discontinued and predisone was substituted in dosages of 5 to 15 mg. per day.

Positive findings on physical examination consisted of obvious psoriasis involving legs, hands, and elbows. There was tenderness and swelling of the right wrist, with slight flexion contracture of both elbows. Several of the metatarsophalangeal joints were tender. Pertinent laboratory data included a sedimentation rate (Westergren) of 45 mm. in one hour, a hematocrit of 44%, serum proteins of 7.2 gm. per 100 cc., with an albumin-globulin ratio of 1. The sheep-cell agglutination titer was 4096. Stools were negative for occult blood. X-ray studies revealed typical changes of rheumatoid arthritis, with joint-space narrowing and bone destruction. The chest x-ray was clear.

The patient was without gastric symptoms until the winter of 1956, when she experienced occasional epigastric pain, usually relieved by milk. A gastrointestinal series performed at the Clinical Center on March 22, 1957, demonstrated an ulcer crater in the antrum of the stomach. (Figs. 7 and 8).

Fig. 7 (Case 4). Anteroposterior film of stomach, demonstrating ulcer crater in antrum.



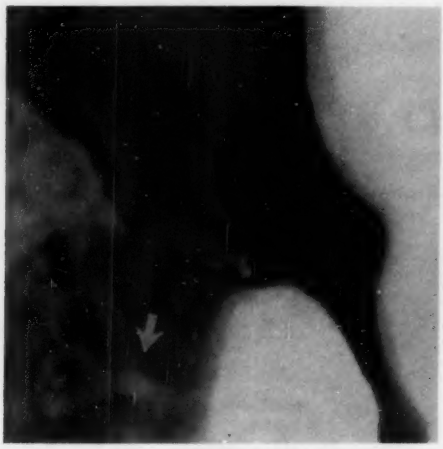


Fig. 8 (Case 4).—Compression spot film of antrum, showing retained barium in crater.

An antiulcer regimen consisting of aluminum hydroxide gel, modified diet, and anticholinergic drugs alleviated her symptoms. A repeat x-ray examination of the stomach on May 2, 1957, demonstrated healing of the ulcer crater.

Comment.—This patient was given corticosteroid therapy for over five and one-half years before symptoms appeared. She demonstrated the fact that patients may go for months or years without gastrointestinal symptoms while given such medication, only to have an ulcer develop (sometimes very rapidly; e. g., Case 5). At fluoroscopic examination of this patient, there were no localized findings, such as irritability, radiating folds, or localized spasm. She did admit to mild tenderness on direct palpation over the ulcer crater.

CASE 5.—A 54-year-old white woman was admitted to the Clinical Center for the first time on May 3, 1956, with a history of polyarthritis since 1939. All peripheral joints were involved during the 17 years of her illness. Previous medication included gold injections, corticotropin, and phenylbutazone (butazolidin). Prednisone was started in March, 1955, at a dosage level of 20 mg. daily, soon reduced to 15 mg. Approximately one year later, April, 1956, compression fractures of T-11, L-1, L-4, and L-5 developed.

Physical examination on admission in May, 1956, showed typical joint changes, consisting of swelling, tenderness, deformity, and pain on motion, especially of the hands. The skin was shiny, and there was a 2+ pitting edema of the legs and feet. Laboratory findings revealed a hematocrit of 40.5%, a sedimentation rate (Westergren) of 15 mm. in one hour, negative L. E.-cell preparations, and normal blood chemistries. The sheep-cell agglutination titer was 128.

The patient was discharged to outpatient status on Aug. 17, 1956, with a continuing daily dose of 15 mg. of prednisone. On Sept, 17, 1956, she was readmitted because of pain across the midback of three weeks' duration. Because of occasional nausea and vomiting, a gastrointestinal series was performed on Dec. 17, 1956, which revealed a hiatus hernia (Fig. 9) as well as an area suggestive of ulceration in the immediate prepyloric area (Fig. 10). The patient was started on an ulcer regimen and was discharged to outpatient status on Dec. 28, 1956. The patient was free of symptoms as far as the gastrointestinal tract was concerned for a brief period but suddenly developed a severe hematemesis on Dec. 31, 1956. She was readmitted to the hospital and treated by transfusion and sedation. Her condition stabilized, and blood pressure was found to be normal. One day later a second severe hematemesis occurred, and the patient was subjected to surgery, with performance of a subtotal gastrectomy. During the operative procedure, she received hydrocortisone and 6 pt. of blood. The patient withstood the surgery well, and her blood pressure was stable during the postoperative period in the recovery room. However, on return to her room, she suddenly died.

Comment.—The lack of tenderness, irritability, edema, and deformity of the

Fig. 9 (Case 5).—Barium-filled stomach, revealing hiatus hernia. Ulcer craters obscured.

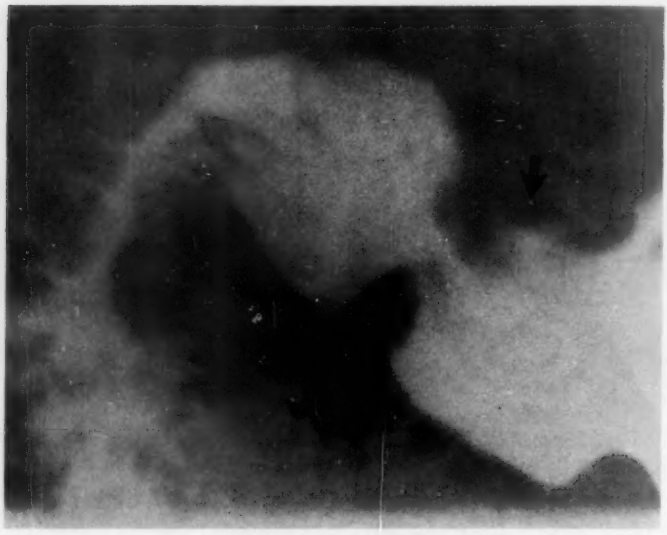


Fig. 10 (Case 5).—Spot film of antrum with mild compression, demonstrating small collection of barium in ulcer crater (proved at surgery).

mucosal folds led to doubt as to the presence of an active ulcer crater. Such a lesion was suspected, however, because of the fluoroscopic observation of a small collection of barium along the lesser curvature and on one of the spot films of this area (Fig. 10). A repeat study was suggested, but owing to sudden and unexpected death, it was never accomplished. This experience confirms the observation that ulcers may progress rapidly with hemorrhage or perforation while corticosteroid therapy is being given. Beck et al.,[1] as early as 1950, reported two cases of acute peritonitis occurring during corticotropin administration—one from an acute perforation of a duodenal ulcer. They emphasize that many of these patients may lack the important signs and symptoms normally encountered in acute ulceration and perforation.

At surgery, a gastric ulcer measuring 1.5 cm. was found in the immediate prepyloric area. An additional acute ulcer measuring 2 cm. in diameter was discovered along the posterior wall of the stomach near the lesser curvature, approximately 3 cm. distal to the esophageal cardiac junction. The margin of this ulcer was extremely sharp, and there was minimal surrounding edema, inflammation, and fibrosis. A bleeding vessel was present at the base of the ulcer at the time of surgery. The stomach wall was very pliable in this area. The prepyloric ulcer was more chronic in appearance but likewise demonstrated a paucity of fibrosis or other evidence of body defense.

Case 6.—A white man aged 64 was admitted to the Clinical Center on Nov. 28, 1955, with a history of polyarthritis dating back to 1926. During the ensuing years, most of the joints were involved. In 1953, the patient experienced epigastric pain and an x-ray of the gastrointestinal tract demonstrated a duodenal ulcer. During the same year, a myocardial infarct occurred from which he recovered. Cortisone was administered from 1954 until May, 1955, at which time the medication was changed to prednisone, 30 mg. daily. This was later reduced to 15 mg. per day.

Physical examination demonstrated soft-tissue swelling, tenderness, and pain on motion of most of the joints of the body. Ulnar deviation of the fingers at the metacarpophalangeal joints and a flexion contraction of the right knee were noted. Positive laboratory findings consisted of a sheep-cell agglutination titer of 8192, sedimentation rate (Westergren) of 70 mm. in one hour, and an ECG showing an old posterior infarct with left axis deviation.

One month after hospitalization, the patient complained of epigastric pain. An upper gastrointestinal examination on Feb. 17, 1956, was reported as negative except for a hiatus hernia. Because of his symptoms, however, the patient was started on an antiulcer regimen with only partial pain relief. He was discharged on May 4, 1956,

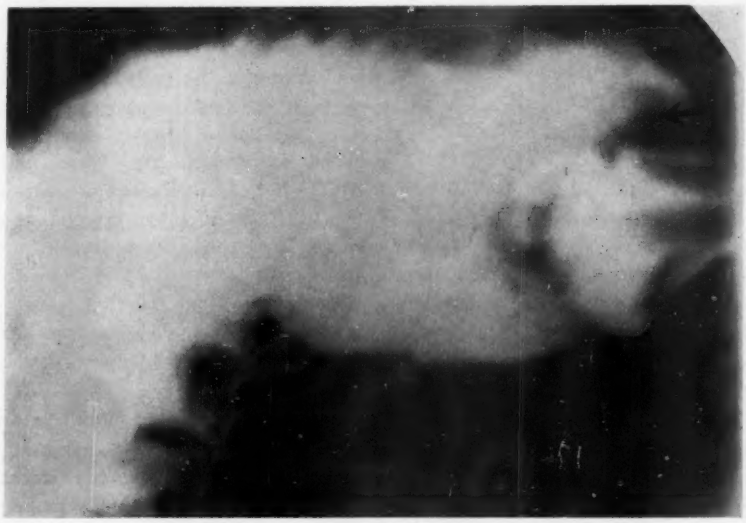
Fig. 11 (Case 6).—Oblique view of stomach, demonstrating a small hiatus hernia. Arrow points to large ulcer crater at apex of duodenal bulb.

with a recommended daily dosage of 15 mg. of prednisone. The patient was given two bottles of medication and unfortunately took 15 mg. of prednisone from each bottle—a total of 30 mg. daily. On a subsequent outpatient visit, he was instructed to reduce this dosage to a total of 15 mg. a day, but he disregarded this advice.

The patient was readmitted on June 30, 1956, complaining of severe epigastric pain, tarry stools, and weakness, and was given 5 pt. of blood. An emergency gastrointestinal series was reported by one of the radiologists as showing no definite evidence of ulceration. The source of the hemorrhage was then assumed to originate from the hiatus hernia. In view of the age and cardiac status of the patient, it was deemed unwise to attempt surgery. On July 6, 1956, following a stable period of freedom from bleeding, a sudden hematemesis resulted in severe shock, and the patient died before blood could be administered. At autopsy, the intestinal tract was filled with blood. A large ulcer crater measuring 3.5×5 cm. was present at the junction of the first and second portions of the duodenum. The base of the ulcer was 1 cm. deep, with walls that were sharply punched out.

Comment.—According to Bockus,[2] only 5% of duodenal ulcers occur at the apex of the duodenal bulb or distal thereto. On review of the films in retrospect, a large ulcer crater (Fig. 11) is demonstrated. An enlarged spot film of the same area (Fig. 12) reveals complete obscuration of the ulcer crater by barium. The radiologist performing the study reported no evidence of tenderness, irritability, or pylorospasm. The large size and location of the crater led to the disregard of its presence. This case serves as a strong reminder that great care

Fig. 12 (Case 6).—Enlarged spot film of duodenal bulb filled with barium, thus obscuring large ulcer crater. Arrows point to base of duodenal bulb.



Peptic Ulcers in Corticosteroid-Treated Patients with Rheumatoid Arthritis *

Case	Age	Sex	Ulcer Site	Duration of Arthritis, Yr.	Daily Dose Prednisone, Mg.	Duration of Steroid Treatment	Other Side-Effects
7 †	16	M	D	3	30	4 wk.	Fracture pelvis
8	28	F	D	11	15	2 yr.	
1	31	F	G	½	15	4 mo.	
2 †	32	F	D	4	30	3 wk.	Psychosis
9	40	M	D	6	10	4 mo. –	
3 †	42	F	D	15	30	4 ½ yr.	Fracture vertebrae, ribs
4	44	F	G	9	7.5	6 yr.	
10	47	M	D	6	30	2 yr.	Fracture ribs
11	51	M	D&G	2	15	2 yr.	
5 †	54	F	G	17	15	14 mo.	Fracture vertebrae
6 †	64	M	D	30	30	2 yr.	
12 †	67	F	D	16	20	5 wk.	Fracture vertebrae

* There were 49 patients treated with corticosteroids, 12 of whom developed peptic ulcers.
† These patients are included in a tabular presentation in an article appearing in J. Chron. Dis. 5:751 June 1957.

must be exercised in examining these patients. The lack of tenderness, irritability, or localized spasm should not lull the radiologist into a false sense of security. Any abnormality, detected fluoroscopically, must be carefully evaluated and recorded by compression and air-contrast spot films as well as conventional films obtained in multiple projections.

Comment

The Table briefly summarizes the case histories of the 12 patients in this series developing ulcers while given corticosteroid therapy. Six of these cases are reported in some detail, since they are considered representative of the various types of lesions encountered in the study. The two patients with fatal hemorrhage are also included in the report, as they emphasize the hazards of peptic ulceration occurring in patients receiving this type of medication.

It can be seen that most of these patients had been receiving prednisone at a daily dosage level of 15 mg. or more. The majority had had other steroids for varying periods before the start of prednisone therapy. The earliest ulcer appeared after three weeks of treatment, while one ulcer occurred after six years of treatment (including hydrocortisone as well as prednisone). Thus, it is evident that peptic ulcers may develop after long periods of "safety" with corticosteroid therapy.

The characteristic history and symptoms of gastric or duodenal ulcer are frequently lacking in patients undergoing treatment with the corticosteroids. Pain, although often atypical, is still the most reliable clinical symptom. Occult blood in the stool likewise has proved to be of great assistance. Silent ulcers may occur, and, in some instances, an unexplained rapidly developing anemia may be the first clue of a peptic ulcer.

An example of the unusual manifestations of peptic ulceration may be cited in the case of a patient with myocosis fungoides not included in this rheumatoid group. Following the administration of a total of 2760 mg. of metacortin, and while the patient was taking 80 mg. of prednisone daily, a routine chest film demonstrated the presence of subdiaphragmatic air. Free intraperitoneal air was confirmed by decubitus films. Physical examination revealed mild abdominal tenderness, and there was elevation in the white cell count and polymorphonuclear cells. The presence of a perforation of the gastrointestinal tract was never proved, as the patient responded well to antibiotics and intravenous fluids and hence was not operated upon. Subsequent studies failed to demonstrate an ulcer. It was the consensus of opinion of all concerned that this patient had a silent ulcer which perforated and subsequently healed without significant scarring.

The fluoroscopic observations in the so-called "steroid ulcer" patients may be briefly summarized:

1. A crater may be the only radiographic evidence of ulceration.

2. Diminished or absent tenderness to palpation is frequently noted. This presum-

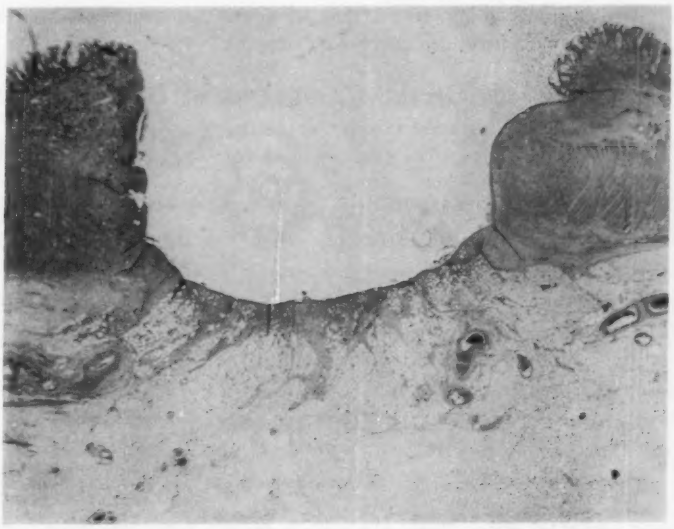


Fig. 13 (Case 5).—Photomicrograph of ulcer crater. Note sharply punched-out borders of lesion, with minimal surrounding tissue reaction.

ably is related to the anti-inflammatory effect of the administered steroid.

3. Distortion of tissue around the ulcer crater is often absent. Edema and inflammation at ulcer site may be diminished by the steroid therapy.

4. Spastic changes, such as an incisura or pylorospasm, are frequently lacking owing to steroid medication.

5. A deformed duodenum may be demonstrated in some cases and, if found in a patient previously shown to have a normal duodenum prior to onset of therapy, may be regarded as presumptive evidence of an ulcer.

A high index of suspicion is well warranted in the examination of a patient receiving corticosteroids and experiencing even vague epigastric pain or with occult blood in the stools. Our experience clearly indicates that many of the usual roentgen signs of peptic ulceration in patients given steroid treatment may be entirely absent. This is important for physicians, and especially radiologists, to appreciate if they are to arrive at a proper diagnosis in those patients with subtle radiological findings and atypical symptoms.

Histologically, these peptic ulcers developing in corticosteroid-treated patients are interesting in that they commonly show very little evidence of surrounding edema and inflammation. The ulcer margins are sharp and punched out. Fibrosis is minimal, and few adhesions or other signs of attempt at tissue repair are encountered. The pathologic findings are consistent with the rapid clinical course of some of these patients, who may suddenly bleed profusely from the gastrointestinal tract after only minimal warning symptoms of peptic ulceration. Figure 13 shows a photomicrograph of Case 5 taken at the site of gastric ulcer. Note the sharply "punched-out" borders of the ulcer crater, which had penetrated through the muscle layer with minimal reaction of surrounding tissues. These findings are characteristic but not pathognomonic of corticosteroid ulcers.

Summary

A total of 12 (24%) of a series of 49 patients treated with corticosteroids for rheumatoid arthritis developed peptic ulceration. The incidence of peptic ulcers is appreciably higher in these patients than in similar patients undergoing other types of therapy for rheumatoid arthritis.

The atypical signs and symptoms of peptic ulceration occurring in these patients merit reemphasis.

The histological picture is that of acute ulceration with little evidence of healing or repair.

Patients receiving corticosteroids deserve careful questioning concerning epigastric distress, and routine stool examinations for occult blood are advisable. Suspicion of possible ulceration requires a thorough and careful search for ulcer crater formation.

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The Gastric and Jejunal Mucosae in Healthy Patients with Partial Gastrectomy

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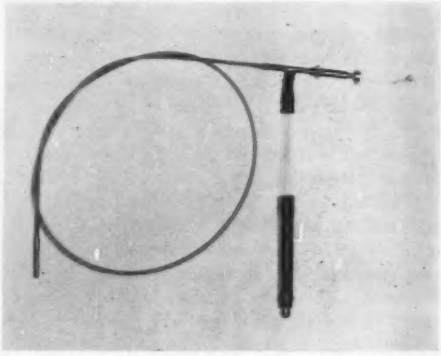
Studies of the gastric and jejunal mucosae may help to throw a light on some of the postgastrectomy syndromes. In this paper we present the detailed results of 41 biopsies done with a suction biopsy tube. Between March and July, 1956, we saw a number of patients who had had partial gastrectomy or gastroenterostomy for benign ulcers during the previous five years. They had been requested to attend the outpatient clinic, and they were asked if they would volunteer for gastric biopsy. Most of those who attended did accept biopsy, whether they had symptoms or not. At the first interview, one of us (L. C. G.) made a clinical assessment of the patient regarding symptoms and general physical status. A completely unbiased analysis of symptoms was recorded before the results of biopsy were known. Some patients did not attend when requested or for the biopsy session, thus no statistical data on a series of cases can be given here because various elements of selection may be implicated.

Here we are concerned only with 41 patients who were found to be fit and well and could be considered to be "normal" or healthy postgastrectomy cases. They had no anemia (hemoglobin over 85%) and no gastrointestinal symptoms apart from mild postprandial discomfort after large meals or after certain foods which the patient had learned to avoid. These minor symptoms may be considered to be "normal" after partial gastrectomy. All those who had severe symptoms after meals, recognizable "dumping syndromes," anemia, diarrhea, weight loss, anorexia, or pain are excluded from this survey. The patients included had not made any recent complaint to their doctors. They were not given a special diet and were taking no alkalis or other medicines. All were working unless retired because of age.

This study is intended to give information which may be used as a basis for further investigations on postgastrectomy syndromes of all types. A comparison with healthy postgastrectomy patients is necessary in these cases.

Biopsies and microscopy were all performed by one of us (F. L.) and, as the patients were "normal" volunteers, only one adequate piece of mucosa was removed in most cases. For the same reason, no uncomfortable tests, such as fractional test meals, were performed.

Fig. 1.—Modified Woods' biopsy tube, with glass and rubber extension on side-tube.



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Winston Churchill Scholarship, Copenhagen, 1956 (Dr. Lees).

From Medical Department B (Prof. E. Meulengracht, M.D., L.L.D.) and Pathological Department (Chief, Dr. B. Vimtrup), Bispebjerg Hospital, Copenhagen. Registrar, Royal Infirmary, Sheffield (Dr. Lees); Senior Resident, Department B, Bispebjerg Hospital, Copenhagen (Dr. Grandjean).

Fig. 2.—Distal end of tube, showing cylindrical knife and end-piece.

Method and Material

Technique was essentially as described by other authors.[1] The biopsy tube is a flexible steel spiral about 100 cm. long and 2.5 mm. in diameter, covered with transparent plastic (Fig. 1). A cylindrical knife is screwed to the end of the operating wire which passes through the tube. The knife fits exactly into a removable cylindrical metal end-piece which has a lateral hole into which the mucosa is pulled when suction is applied (Fig. 2). The knife moves to and fro past the hole when manipulated by the wire. Suction is applied via a lateral tube, the lumen of which is continuous with that of the biopsy tube, which is practically air tight.

Preparation of Patient.—A period of four hours of fasting was usually sufficient, but most patients fasted overnight, no other preparation being required. A tetracaine (Decicaine) lozenge was given and 2% tetracaine (amethocaine) was painted on the fauces before the tube was passed, but this was found to be unnecessary and was frequently the cause of much coughing and an inability to swallow food or even saliva for an hour or more. In many cases the local anesthetic was, therefore, omitted.

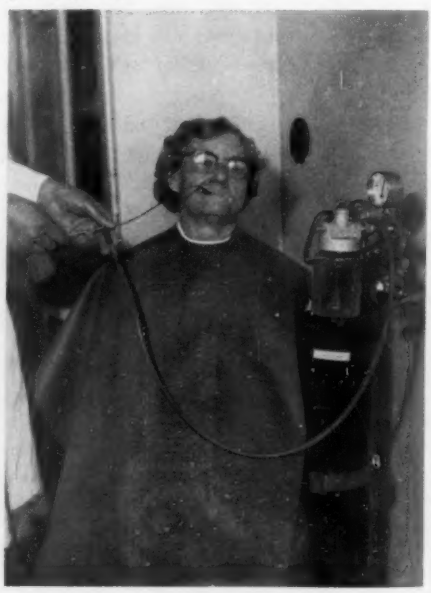
Procedure.—The knife was placed in the "closed" position covering the lateral hole and the tube passed with the aid of a wooden tongue depressor into the esophagus and then the stomach. A swallow or deep breath by the patient often helped its passage, especially if a temporary hold-up occurred at the cardia. When the tube was well down and impinged on the stomach wall, the knife was pushed to the "open" position; suction was applied for a few seconds, and then the knife was pulled to cut off the mucosal specimen which had been drawn in. It was usually quite easy to "feel" the mucosa being cut. Excess stomach secretion passed up the tube and was seen passing through the glass segment of suction tube. This frequently caused a little delay in the drawing in of the mucosal specimen. Sometimes a slight rotatory movement or a withdrawing of the tube caused a contact to occur more quickly.

The occasional failure to obtain a specimen was most commonly caused by a thick mucus blocking the tube. This was remedied by washing out the stomach with dilute solution of sodium bicarbonate prior to another attempt at biopsy. Further specimens are obtainable at one session by discontinuing suction, moving the tube a little, and repeating the biopsy procedure. Suction must be stopped before withdrawing the tube, and the knife must be kept at the "open" position in case mucosa is still adhering. Immediately after withdrawal the end-cylinder and knife were unscrewed and the specimens, removed. The specimens were placed on a small piece of paper to allow easy handling before being put in the fixing solution.

For positioning the end of the biopsy tube one may recruit the help of the radiologist, especially for jejunal biopsies, but often the position of the tube can be gauged by experience. One noticed that jejunal mucosa felt "soft" when being cut, compared with gastric mucosa.

Cleaning the Tube.—This was done by sucking large amounts of water through, followed by acetone and then ether—to dry it. The knife and end cylinder were treated in the same way. It was washed in cetrimide (Cetavolon) solution before use. Suction was obtained by a compressed air

Fig. 3.—Biopsy tube in use, with compressed air suction apparatus. Traction is being exerted on operating wire.



suction pump (Fig. 3), and any aspirated stomach contents could be tested for free acid. The pressure required was determined by experience. A water pump is equally satisfactory.

After the biopsy the patient was allowed to go home and asked to report to us should anything untoward occur, e. g., melena, but no trouble was reported. There were no complications.

The biopsy specimens were normally full thickness to the muscularis mucosae and about 2 to 4 mm. in diameter. No case is included which could not be fully assessed histologically. Specimens were immediately placed in a mixture of 20% formalin, 20% mercuric chloride, and isotonic saline to 100% and were later prepared by Dr. Vimtrup. Stains used were iron hematoxylin, Van Gieson hematoxylin and eosin, and Delafield's hematoxylin. Four to six sections were made of each specimen.

Histological assessment was made at least twice, along with about 250 other gastric and jejunal specimens, so that there was a very unbiased analysis. In no case was the patient's name or clinical details known at either the first or second microscopic examinations, and preparations from many different conditions were being seen at random.

Results

Gastric Mucosa.—For the purpose of an over-all general analysis the histological appearances may be divided into normal, slightly abnormal, or severely abnormal. A normal specimen shows a well-defined surface layer of regular columnar cells. There are only a few interstitial cells (substantia propria), comprising mainly plasma cells and lymphocytes, with occasional polymorphonuclear leukocytes. There are well-packed fundic glands with chief and parietal cells. Slight changes include a moderate excess of interstitial cells in the superficial zone, at the level of the necks of the glands, or scattered throughout the mucosa. An abnormal irregular surface or distortion of the foveolae are also regarded as minor abnormalities. There is no atrophy. Severe changes are severe infiltration, definite atrophy of the gland elements, intestinal metaplasia, or the presence of pseudopyloric glands. Severe foveolar corkscrewing may be seen too. In most specimens there are combined changes. Changes of shrinkage, edema, and hemorrhage have been discounted in the analysis, for, although they may be real abnormalities, they could equally well be artifacts produced by suction. The same applies to casts of fundic gland elements which were often present. When bleeding obscured the histological picture the specimen was excluded. Examples of histological findings shown in Figures 4 to 9.

Only one case showed a very normal gastric mucosa, a man aged 41 years. Ulcer symptoms had been present since 1943. He had a Billroth Type 1 gastrectomy for duodenal ulcer in May, 1953. A scar of a

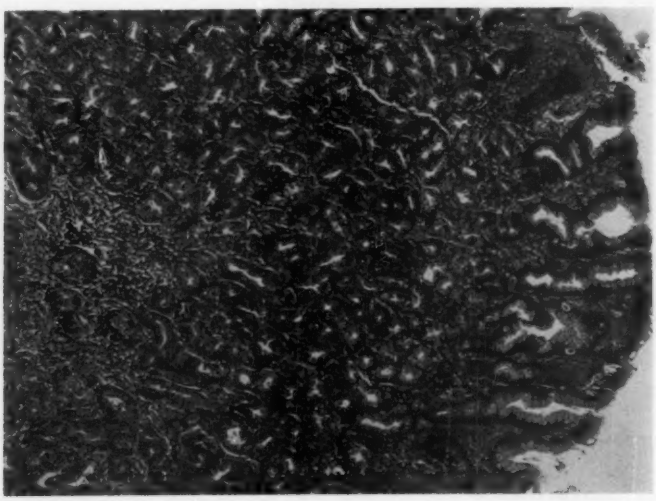


Fig. 4 (Case 10).—Biopsy specimen. Normal surface. Moderate superficial and deep infiltration. Well-packed normal glands. No atrophy; × 80.

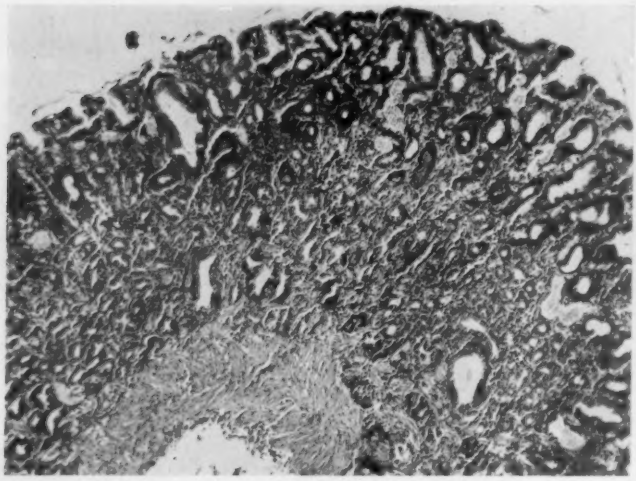


Fig. 5 (Case 27).—Biopsy specimen. Full thickness. Irregular foveolae. Severe superficial and deep infiltration. Moderate degree of atrophy; × 60.

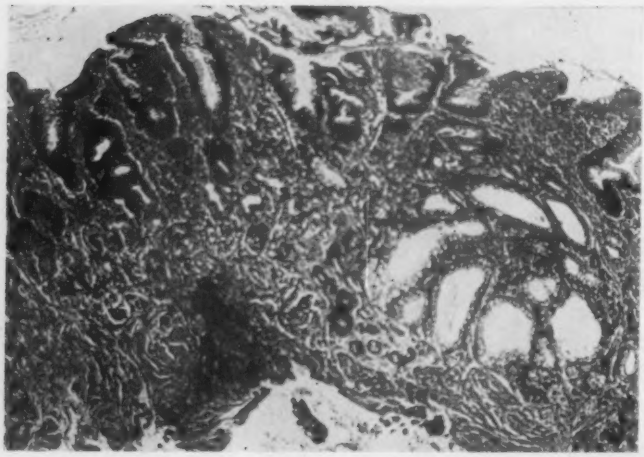


Fig. 6 (Case 23).—Biopsy specimen. Full thickness. Irregular surface. Moderate superficial and deep infiltration. Moderately severe atrophy, with a group of dilated pseudopyloric type glands; mag. × 80.

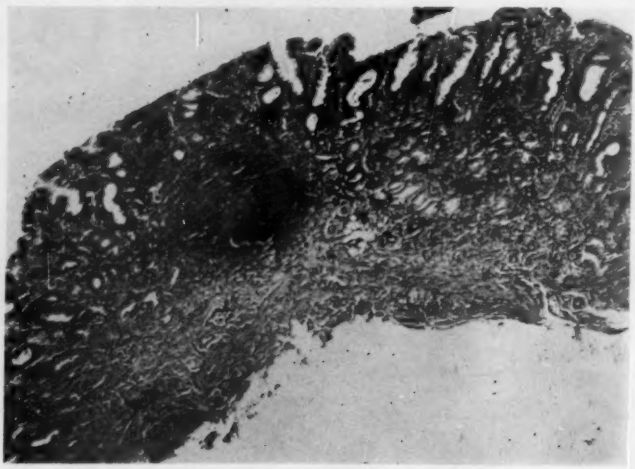


Fig. 7 (Case 28).—Biopsy specimen. Full thickness. Irregular surface. Severe superficial and deep infiltration. Severe atrophy. One lymphocyte collection; × 60.

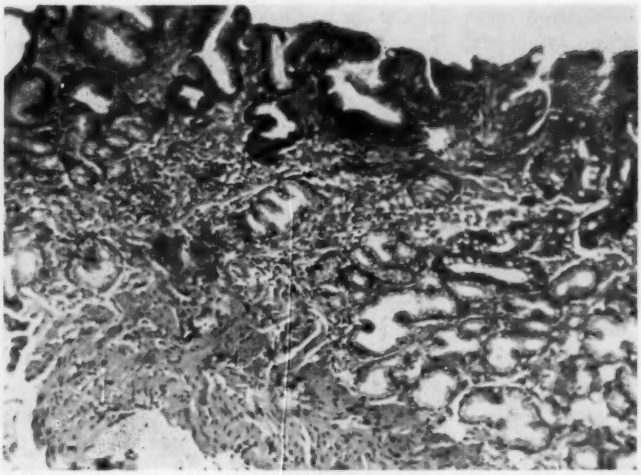


Fig. 8 (Case 13).—Biopsy specimen. Full thickness. Irregular surface. Distorted foveolae. Mild superficial and deep infiltration. Complete atrophy. Pseudopyloric glands and intestinal metaplasia; × 100.

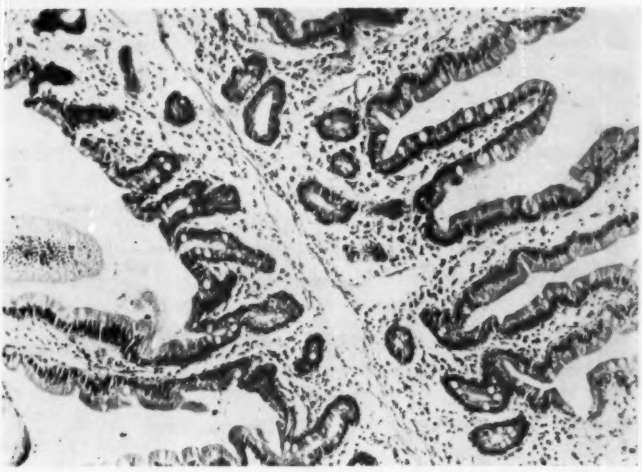


Fig. 9 (Case 36).—Jejunal mucosa. Normal degree of cellular infiltration.

TABLE 1.—*Data on Ten Patients with Slight Changes in the Mucosa*

Case No.	Sex	Age	Dyspepsia Began	Operation Date	Surface Layer	Superficial Infiltration	Deep Infiltration	Foveolae	Lymphocyte Aggregations
2	M	57	1941	Jan., 1951	Irregular	Moderate; some PMN	Nil	Some corkscrewing	0
3	M	56	1937	Sept., 1951	Normal	Moderate chronic	Nil	Normal	0
4	M	42	1943	Nov., 1951	Normal	Moderate chronic	Mild chronic	Normal	1
5	M	43	1949	Feb., 1952	Irregular	Mild chronic	0	Considerable corkscrewing	0
6	M	35	1937	June, 1952	Irregular	Moderate chronic	0	Irregular	2
7	M	69	Many years ago	Aug., 1953	Normal	Mild chronic	0	Normal	0
8	M	53	1930	1940–1953	Normal	Mild chronic	Mild chronic	Normal	0
9	M	46	Not Known	1953	Normal	Moderate; some PMN	0	Normal	1
10	M	54	1929	April, 1954	Normal	Moderate chronic	Moderate deep	Normal	1
11	M	40	1945	Aug., 1955	Normal	Moderate chronic	Moderate deep	Normal	0

lesser curvature gastric ulcer was also present. At follow-up he had no symptoms except abdominal discomfort if he ate a large hot meal. Biopsy showed a very slight superficial infiltration and was considered to be quite normal fundic mucosa (Case 1).

Ten patients had slight changes in the mucosa, consisting of one or more of the following features: an irregular surface layer of cells, distortion of the gland foveolae, and moderate superficial infiltration with plasma cells, lymphocytes, or polymorphonuclear neutrophils. Some also had lymphocyte aggregations. No atrophy was present. Details are shown in Table 1. All 10 had had a Polya type gastrectomy. Case 8 had had a previous gastroenterostomy, in 1940. All had duodenal ulceration. Case 8 had also had a marginal ulcer. These patients had no serious symptoms. Case 2 drank five to six bottles of beer a day. Case 6 was "upset" by rhubarb. Case 7 had epigastric discomfort after large meals, and Case 10 had occasional postprandial vomiting.

Twenty-two patients had severe abnormalities in the gastric mucosa, the details of which are recorded in Table 2. None had severe symptoms. Case 13 had a moderate degree of hepatic cirrhosis at operation and preferred small meals. He was the only one who showed complete mucosal atrophy, with intestinal metaplasia, pseudopyloric glands, and Paneth cells. Case 14 was taking iron intermittently to avoid anemia but had no symptoms. Case 17 had slight abdominal discomfort after a lot of milk foods, and the gland cells showed a vacuolated appearance, which was also seen in Cases 25 and 29 and was thought to be an expression of some kind of secretory activity. Case 18 avoided

TABLE 2.—*Data on Twenty-Two Patients with Severe Abnormalities in the Gastric Mucosa*

Case No.	Sex	Age	Dyspepsia Began	Diagnosis	Operation Date	Surface Layer	Superficial Infiltration	Deep Infiltration	Foveolae	Lymphocyte Aggregations	Degree of Atrophy	Pseudopyloric Glands
12	F	68	1949	G. U.	Oct., 1951	Irregular	Severe	Severe; some PMN	N	1	Mod.	0
13	M	67	1934	G. U.	May, 1951	Irregular	Mild	Mild	Distorted	0	Complete	Many
14	M	55	1931	D. U.	March, 1951	Irregular	Mod.	——→	N	1	Almost complete	Many
15	M	43	1935	D. U.	July, 1951	Irregular	Mod.	Severe; some PMN	Severe corkscrewing	0	Mod.	0
16	M	40	1934	D. U.	March, 1951	Irregular	Severe	Mod.	N	0	Mod.	Some
17	M	30	1944	D. U.	Sept., 1951	Irregular	Mod.	Mod.	Some corkscrewing	2	Mod.	0
18	F	63	1946	Pyl. Canal.	Jan., 1952	Irregular	Severe	——→	Some corkscrewing	2	Mod.	0
19	M	54	1946	D. U.	1952	Irregular	Severe; PMN+	0	N	0	Mod.	0
20	M	76	1933	D. U.	Jan., 1953	Irregular	Severe	——→	Some corkscrewing	0	Mod.	2 groups
21	M	60	1945	D. U.	May, 1953	Irregular	Severe; some PMN	0	Severe corkscrewing	0	Rather severe	Many
22	M	57	1947	D. U.	May, 1953	Irregular	Severe; few PMN	——→	0	0	Mod.	0
23	M	47	1943	D. U. G. U.	July, 1953	Irregular	Mod.	——→	Distorted	0	Mod. severe	Some
24	F	25	1945	D. U.	Oct., 1953	Irregular	Fairly severe	——→	Distorted	2	Mod.	Some
25	F	57	1943	G. U.	Nov., 1954	Irregular	Mod.	Slight	Distorted	2	Mod.	Some
26	M	64	1943	D. U.	Aug., 1954	Irregular	Rather severe	——→	N	0	Mod.	0
27	M	59	1945	G. U.	Aug., 1954	Irregular	Severe some PMN	——→	Irreg.	0	Mod.	0
28	M	52	1932	D. U.	Feb., 1954	Irregular	Severe	——→	Irreg.	0	Severe	0
29	M	42	1947	G. U.	May, 1954	Irregular	Severe	——→	Irreg.	1	Mod. severe	Some
30	M	41	1941	D. U.	Jan., 1954	Normal	Severe	——→	N	0	Slight	0
31	M	75	1945	D. U.	Aug., 1955	Irregular	Mod.	——→	Irreg.	0	Severe in half	0
32	M	64	Short hist.	D. U.	May, 1955	Irregular	Mod. severe PMN	——→	Some C. S.	1	Mod.	Some
33	M	46	1948	D. U.	Aug., 1955	Normal	Mod. or severe	——→	Some C. S.	2	Slight	0

milk foods, and Case 23 noted some slight discomfort after milk or chocolate. Case 30 was moderately alcoholic, and Cases 31 and 32 had discomfort after excessively large meals. All 22 cases had had a Polya type operation, except Case 20 (anterior gastroenterostomy) and Case 24 (Billroth Type 1). Case 31 had a Polya gastrectomy in 1955 after a gastroenterostomy in 1929. Intestinal metaplasia was seen only in Case 13, and a collection of fat cells, only in Case 28. All those with severe changes had some degree of atrophy, pronounced in three cases. Pseudopyloric glands were associated with very severe changes. Those who had dilated glands lined with flat epithelium could be described as having "cystic gastritis" in two cases. Flattened or distorted cells on the surface of the mucosa tended to occur in the more abnormal group of cases. This also applies to gross corkscrewing of the foveolae. Excess polymorphonuclear neutrophils were present in five mucosae, and six had noticeable eosinophilic infiltration amongst the other cells.

Correlation of mucosal changes and length of time since operation showed the following results. One normal mucosa: operation in 1953. Slightly abnormal mucosae: operation in 1951, three cases; 1952, two cases; 1953, three cases; 1954, one case, and 1955, one case. Severely abnormal mucosae: six cases operated on in 1951; two, in 1952; five, in 1953; six, in 1954, and three, in 1955. No definite conclusion could be drawn regarding mucosal changes and lapse of time since operation.

Regarding the type of operation, we note that the only normal mucosa was in a Billroth 1 resection, but another of the same type showed severe changes. All those with active gastric ulcer at operation were in the "severely abnormal" group. Of the 10 cases with slight mucosal changes, 9 had had a chronic duodenal ulcer and 1 an anastomotic ulcer. The rest of the duodenal ulcer cases (except Case 1) were in the group with severe changes.

Of those patients between 60 and 75 years at the time of biopsy, 2 had slight and 8 had severe changes, whereas of those between 26 and 60 years, 1 was normal; 8, slightly abnormal, and 14, severely abnormal. It is probable that grosser abnormalities are more likely to be seen in the older patient.

In the seven patients from whom two pieces of mucosa were taken, there was good histological correlation between the two specimens in each case.

Jejunal Mucosa.—Only a brief review is necessary, because the histological appearances were normal in all except possibly Cases 37 and 40, who had perhaps a slight increase in plasma-cell concentration in the substantia propria. This was probably within normal limits. Case records are summarized in Table 3. All had duodenal ulceration before operation, and in addition, Case 35 had a gastric ulcer scar. Operations performed were of Polya type, except in Case 34 (Billroth 2), and Case 41 had a Polya-Hoffmeister. Case 40 had occasional vomiting after big meals, and Case 41 had slight postprandial discomfort but needed no treatment. The rest had no symptoms.

Comment

The gastric mucosal specimens showed "severe" changes in 22 cases of 33. There were 10 cases with milder changes, but even these may be important. A similar investigation was reported by Palmer[2] on 45 subjects from whom 5 jejunal specimens were also obtained. He found that eight had glandular atrophy and many had foveolar changes and degeneration of cells in the neck region. A heavy diffuse round-cell infiltration was consistently present from the neck

TABLE 3.—*Data on Eight Patients from Whom Jejunal Specimens Were Taken*

Case No.	Sex	Age	Date of Operation
34	M	59	1953
35	M	61	1951
36	M	58	1952
37	F	81	1953
38	M	53	1953
39	M	42	1953
40	M	66	1953
41	F	39	1955

level to the surface, mainly consisting of plasma cells and lymphocytes with occasional polymorphonuclear neutrophils and eosinophils. Ten cases had surface disease. Palmer also mentions transepithelial leukopedesis, which was commonly seen in our specimens too. An even regular corkscrewing of foveolae was a typical change. A control series of 105 subjects without gastrointestinal symptoms showed "a remarkable degree of normality," which implies that comparatively minor changes may be important.

Joske, Finckh, and Wood [3] also reported 44 biopsies of gastric mucosa after partial gastrectomy or gastroenterostomy. Fourteen specimens were normal. Fifteen had superficial gastritis without atrophy, and four had superficial gastritis with some degree of atrophy. Six had atrophic gastritis (50% loss of gastric glands), and one had complete gastric atrophy. The histological appearances were not correlated with symptoms, although the authors believe that gastritis in such patients may be a cause of symptoms, which is often neglected or not considered by the clinician.

On the whole our biopsy specimens seem to show severer changes than those of Palmer. The following factors may account for this: 1. Only one-ninth of his cases were over 60 years of age, compared with ten-thirty-thirds of our patients who underwent gastric biopsy. 2. The time since operation was different in some of our cases—approximately 1 to 5 years—compared with 2 to 1612 weeks in his. 3. His cases were all shown to have normal gastric mucosa prior to operation, whereas no data are available on this point in our survey.

As for the jejunal biopsies, our eight specimens and Palmer's five were normal in spite of the fact that four of his cases were shown to have gastritis.

The only factor common to all the subjects is a gastrojejunal stoma, which suggests that regurgitation of jejunal contents into the gastric stumps might be the cause of the mucosal changes. Gastric biopsy specimens from cases of active duodenal ulcer rarely show any degree of atrophy and usually a minimal superficial infiltration in our experience. This suggests that the stump mucosal changes occur after operation. It is not known whether the "gastritis" or "atrophy" are progressive.

Some possible implications of these findings may be considered. A completely atrophic mucosa may belong to the type of case liable to develop pernicious anemia at a later date; it is unlikely to belong to a case of anastomotic ulceration because of lack of acid secretion. Even a moderate atrophy might protect the patient from anastomotic ulceration—in this case one might consider that atrophy is desirable.

Severe gastritis with or without atrophy in the stump does not cause symptoms which disturb the patient unduly, but these patients are accustomed to slight symptoms, which they learn to ignore, and, therefore, one cannot conclude from this study that such gastritis would not cause symptoms in others.

Summary

The histological findings in a series of "normal" or healthy "postgastrectomy" patients are described with clinical details. The gastric mucosa showed abnormalities in many cases; in two-thirds of the specimens the changes were severe. The jejunal specimens were essentially normal in appearance.

The findings may be useful for comparison with various types of postgastrectomy syndrome. It cannot be assumed that mucosal disease is the cause of symptoms. Possible implications of our findings are mentioned.

Prof. E. Meulengracht gave help and advice and allowed us to investigate his patients; Prosektor B. Vimtrup provided assistance, and Sister E. Culmsee helped at all the biopsy sessions.

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Addendum

Although an insufficient number of patients with postgastrectomy syndromes have as yet been investigated, it is perhaps worth

recording that in four with anastomotic ulceration and acute bleeding there was no mucosal atrophy at all.

Of four thought to have iron-deficiency anemia without ulceration, two had moderate atrophy and two had none.

One with steatorrhea had slight, and another, complete atrophy. Three with dumping syndrome alone showed slight and moderate atrophy. All showed excessive inflammatory infiltration. Many more cases are required before a proper assessment can be made.

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Syphilis

Review of the Recent Literature

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(Concluded from page 823)

Congenital Syphilis

Congenital Syphilis in One of Twins.—Laird [97] presents two case reports of congenital syphilis occurring in only one of binovular twins, of which the first case appears very clear-cut. He concludes that the placental passage of treponemes from the mother to the fetus probably depends on chance and that infection of only one twin is a reasonable, although uncommon, happening, and more likely to ocur in binovular than in monovular twins. Criteria for establishing this phenomenon are discussed.

Congenital Syphilis in Absence of Positive Blood Tests in the Mother.—A detailed report of a case of congenital syphilis in which the diagnosis was clouded by the absence of a reactive serologic test for syphilis in the mother was recorded by Fiumara and Hill.[98] They confirmed their diagnosis when the reaction to the T. pallidum immobilization test on the mother's blood was found to be positive. This is an example of a definite indication for the TPI test, namely, to assist in the diagnosis of syphilis in a patient with epidemiologic evidence of the disease but with negative clinical and serologic findings.

Radiology in Late Congenital Syphilitic Nerve Deafness.—Forty-six congenital syphilitics between the ages of 9 and 53 years of age, six of whom had syphilitic nerve deafness, were subjected by Morton [99] to special radiologic studies. In no case was any significant change seen on x-ray in the appearance of the semicircular canals, cochleae, internal auditory canals, or the bone adjacent to these structures. Morton feels that these negative findings support his theory that late congenital syphilitic nerve deafness is a hypersensitivity phenomenon and suggests treatment with cortisone early in the course of the deafness, before irreversible changes have occurred.

Third-Generation Syphilis.—Szegö [100] describes a case of third-generation syphilis seen at the Komitatsspital, Nyiregyhaza, Hungary. Only 68 such families which conformed to the strict criteria laid down by Finger and Fournier have been described. In Szegö's case a 41-year-old mother and her 6-year-old daughter were found to have congenital neurosyphilis. The child's maternal grandmother was known to have had many miscarriages, and only her three youngest children survived, all of whom had congenital syphilis. The husband of the mother (the child's father) was found to be free from syphilitic infection. Some syphilitic stigmata were found in both mother and daughter, and it is thought noteworthy

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that the main lesions in both cases were confined to the central nervous system, suggesting that some constitutional factor influencing the site of the lesions may have been concerned. Masterson [101] presents a detailed study of 35 of 36 surviving members of a family in which third-generation syphilis was demonstrated. Four generations were included in the investigation, and TPI tests were performed. The Fournier-Finger requirements for diagnosis of third-generation syphilis have been fulfilled except for absence of clinical evidence of infantile congenital syphilis in the patient of the third generation. Sundal and Vogelsang [102] report an example of third-generation syphilis. The serological tests indicated passively transferred maternal reagins, which reverted to seronegativity in the usual way within one month after delivery, before therapy could have influenced them. The diagnosis was made on the basis of a generalized syphilitic metaphysitis in progress. This may be a bona fide case, but we would expect the titer in an infant that is supposed to have syphilitic metaphysitis to be high or rising rather than to revert to the nonreactive state before treatment could have any effect.

Cardiovascular Syphilis

Trends in Cardiovascular Syphilis.—According to the records for 1945 to 1954 of the Los Angeles County Hospital, 1002 persons were admitted during that period with diagnosis of "cardiovascular syphilis," "blood vessel syphilis," and/or "aneurysm of thoracic aorta." Rimsa and Griffith [103] found that charts of 954 of these patients were sufficiently detailed for analysis. They discovered that in that period (1945 to 1954) the incidence of cardiovascular syphilis decreased approximately 47%. Of the patients, 26.8% were found to have syphilitic aortitis; 49.5%, syphilitic aortic insufficiency; 9.3%, syphilitic aortic insufficiency associated with aortic aneurysm; 14.0%, syphilitic aortic aneurysm. The commonest complication was congestive heart failure, followed by hypertension and angina pectoris. Blood serologic reactions for syphilis were positive or repeatedly doubtful in 82% of all patients studied. Radiologic findings were normal in only 8.8% of 633 patients examined. Normal electrocardiograms were obtained in less than 4% of patients examined. No electrocardiographic pattern pathognomonic of cardiovascular syphilis was encountered. Penicillin was confirmed as the drug of choice for the treatment of cardiovascular syphilis; progression of cardiovascular lesions was halted (as evidenced by radiologic examination), and untoward reactions were less frequent than were reactions following adequate therapy with bismuth and/or arsenical compounds. Prognosis as to long-time survival was best in the younger persons.

Aneurysms Complicated by Pregnancy.—Aneurysms of the Aorta and Its Major Branches: Pedowitz and Perell [104] found seven cases with syphilitic saccular aneurysms among their patients with aneurysms of the aorta complicated by pregnancy.

Clinical Manifestations of the Unperforated Aortic Sinus Aneurysm.—Acquired aneurysms of the aortic sinuses of Valsalva are rare and are usually due to syphilis or to bacterial endocarditis. Over a 10-year period more than 2500 patients have been studied by intravenous angiocardiography by Steinberg and Finby.[105] Of these, 19 were found to have unperforated aortic sinus aneurysm. Seventeen of these cases have been reported previously. Ten of the nineteen were syphilitic in origin, the other nine being congenital rather than acquired aneurysms. The aim of this study was to determine whether any salient clinical characteristics existed which would permit more diagnoses being made of this disorder during life. No unique symptomatology was discovered. However, it was learned that if a fusiform saccular aneurysm seems to extend into the heart and, in addition, linear calcifications exist in the region about the aortic sinus, the diagnosis of syphilitic aneurysm of the aortic sinus of Valsalva is almost cer-

tain. This condition may be prevented by early diagnosis of syphilis. It is amenable to surgery. After five years, 3 of the 10 patients with syphilitic aneurysm were known dead, 4 were alive and well, and 3 were lost to observation. Similar findings were made for the nine congenital aneurysms. Harris [106] reviewed the literature concerning aneurysms of the sinus of Valsalva and reported such a case. This particular patient suffered from the rare complication of rupture of a syphilitic aneurysm of the aortic sinus into the right ventricle. The interesting features in this case were that the aneurysm was large, was located in the region of the right cardiophrenic sinus anteriorly, did not actively pulsate, and contained calcium within its walls.

Neurosyphilis

Changing Pattern of Neurosyphilis.—Kofman [107] reviewed 180 cases of neurosyphilis seen at Toronto General Hospital during the four years prior to his report. Three of these cases were dropped later for lack of data. The remaining 177 patients were distributed as follows according to involvement: tabes dorsalis, 56; asymptomatic (spinal fluid changes only), 43; general paresis of the insane, 32; meningovascular, 17; papillary involvement only, 14; taboparesis, 4; absence of ankle jerks only, 4; optic atrophy only, 4; and congenital neurosyphilis, 3. Some interesting cases among these are selected and discussed in detail. Trends in the clinical pattern in neurosyphilis before and after the advent of penicillin are discussed. The effectiveness of penicillin in the various stages of neurosyphilis is evaluated; it is said that a program of treatment with 7,000,000 to 10,000,000 units of penicillin will cure most cases of neurosyphilis and make the spinal fluid and blood seronegative. If repeat doses are necessary, 15,000,000 units of penicillin may be given over a period of eight weeks.

General Paresis.—Fröshaug and Ytrehus [108] studied 855 patients with general paresis admitted to either the psychiatric department of Oslo City Hospital (Ulleval) or the Dikemark Mental Hospital, during the period Jan. 1, 1915, to Dec. 31, 1954. However, the 549 patients with paresis admitted during the periods 1918 to 1938 and 1945 to 1954 are the subject of a special investigation to compare paresis in the period before and after the introduction of malaria therapy and after World War II. These patients are said to give a representative picture of general paresis in Oslo. Some highlights of the findings are as follows: Of these patients, 68.7% were between the ages of 31 and 50 when admitted. Average age of patient at time of infection was 26.2 years; at time of admission, 45.4 years. The average incubation period was 16.7 years for women, 15.8 years for men. Only 13 of these patients had received adequate antisyphilitic treatment. Skilled labor was the most frequent (31%) occupation. As to admission, patients with initial paresis formed 11.8% of all admissions; dementia, 48%; megalomania, 7.1%; paralyses, 15.3%; stupor or delirium, 9.1%; and schizophrenia, 8.4%. Over the years, the duration of symptoms before admission has become shorter. Transfers from other hospitals comprised 23.5% of these cases. Thirty-six per cent of them were discovered by routine serum control and by examination of spinal fluid of seropositive patients.

Lower Urinary Tract in Treated Neurosyphilis.—A study was conducted by Bogash and his colleagues [109] at the University of Pennsylvania to evaluate the urologic status of patients with proved neurosyphilis who had received penicillin treatment. Of the 41 patients, 33 were male and 8, female. Their mean age was 52.9 years. The techniques used consisted of history taking, physical examination, urethrocystoscopy, and cystometry. Fourteen were considered normal, eighteen showed impaired proprioceptive sensitivity of the bladder, and nine showed some other type of vesicular dysfunction. Eleven of the eighteen patients with impaired proprioceptive of the bladder

manifested tabetic pains, as compared to four of the remaining twenty-three patients. Six patients showed impaired voluntary control, fifteen showed some amount of residual urine, and twenty-four gave evidence of intravesicular obstruction. No relationship was found between impaired proprioceptive sensitivity and the severity of the neurosyphilis as measured by the impairment of postural and fibratory sensations, impaired tendon reflexes, ataxia, and pupillary dysfunction. No relationship was found, also, between impaired proprioceptive sensitivity and duration of the neurosyphilis or between the impaired proprioceptive sensitivity and the spinal fluid findings and blood serology.

General Therapy

There has been but little change in the recommendations for therapy of syphilis during this review period. Evan Thomas,[110, 111] in two excellent papers, has summarized and codified much of the present-day "standard" therapy for the various phases of the disease. Perhaps the confirmation of the value of benzathine penicillin G by Smith and his associates [112] represents the chief advance in this field. In his review of the recent literature on the treatment of syphilis, Thomas [110] quotes Smith et al.[112] to the effect that a single treatment with 2,400,000 units of benzathine penicillin G (Bicillin) is just as effective as multiple treatments with 4,800,000 units or more of PAM in recent syphilis. For neurosyphilis or cardiovascular syphilis, three treatments with benzathine penicillin G at 2,400,000 units each are recommended, while, for the same disorders, one requires 6,000,000 to 10,000,000 units of PAM. Also reviewed is the evaluation of treatment of early and late syphilis and the occurrence of penicillin reactions. For the treatment of penicillin-resistant cases, the recommended treatment is 3 or 4 gm. of oxytetracycline or chlortetracycline daily for 10 days or carbomycin (Magnamycin) at a dose of 2 to 3 gm. daily for 10 days in early syphilis. Carbomycin is recommended at the same dose, but for 15 to 20 days, in neurosyphilis or cardiovascular syphilis. Attempts to substitute the older metal therapy with arsenic or bismuth for penicillin can be mentioned only to condemn them unless antibiotics are unavailable or have failed to arrest syphilitic activity. By means of questions and answers, the following phases of syphilis are discussed briefly by Taggart and Ballinger [113]: Routine serologic tests, interpretation of serologic tests, the specific test, reinfection syphilis, masking of syphilis by current use of antibiotics, and treatment of the patient who is allergic to penicillin. Belden [114] presents very briefly his suggested schedules of treatment, post-treatment observations, and indications for re-treatment. Antibiotics other than penicillin may be used to treat syphilis in patients sensitive to penicillin. Oxytetracycline (Terramycin) hydrochloride, chlortetracycline (Aureomycin) hydrochloride, chloramphenicol (Chloromycetin), erythromycin (Ilotycin), erythromycin (Erythrocin) stearate, and carbomycin are effective antisyphilitic agents. It is doubtful that minimal effective dosages of the antibiotics other than penicillin have been determined, but Thomas [111] recommends the following for the penicillin-sensitive patient: Early and latent syphilis should be treated orally with at least 3 to 4 gm. daily of oxytetracycline hydrochloride or chlortetracycline hydrochloride for 10 or 12 days. Individual doses of 0.75 to 1 gm. every six hours are advised. Late symptomatic syphilis, especially neurosyphilis and cardiovascular syphilis, should be treated with similar doses for at least 15 days. In giving such large doses, every effort must be made to avoid gastrointestinal symptoms; however, antibiotics should always be preferred to treatment with arsenicals and bismuth. Despite the lack of conclusive data on the use of carbomycin, treatment might well be tried with 2 to 3 gm. of this antibiotic given daily for periods previously suggested. King [115] believes that the advances in the treatment of venereal diseases occurring

during the three years since 1953 have pertained to better understanding of existing remedies rather than the discovery of new remedies.

Prophylaxis

Diagnosis, Prophylaxis, and Treatment of Congenital Syphilis in Russia.—Pashkov,[116] of the Moscow Medical Institute of Stomatology, describes the early and late clinical manifestations of congenital syphilis, including osteochondritis, diffuse syphilitic infiltrate about the mouth, keratitis, dental stigmata, bone and joint lesions, and neurological involvement. These descriptions are consonant with those made by Western authors. However, the recommended treatment bears no relationship to that used in the United States today. "Penicillin, salvarsan, bismuth, mercury, iodine, etc." are used. Children with early congenital syphilis are given six "courses" of treatment, "four of penicillin and two combined." Children with late congenital syphilis receive eight "courses" of therapy, "five of penicillin and three combined." Control measures in Russia include preventive treatment to all children born to syphilitic mothers who have had inadequate treatment and follow-up of these children for five years after treatment, prenatal examinations, examination of all children born to syphilitic mothers, reporting of all syphilis cases or suspicious cases of congenital syphilis to venereological institutions, examination for congenital syphilis of all children in children's homes and boarding schools, and thorough clinical and spinal fluid examination before marriage of former congenital syphilis patients.

Treatment of Early Syphilis

According to Thomas,[111] a single treatment with 2,400,000 units of benzathine penicillin G (Bicillin, Permapen) is advised for routine treatment of early symptomatic syphilis. This dosage is best given by an injection of 1,200,000 units (4 cc.) in each buttock. A single injection of 4 cc. of a preparation containing 600,000 units per cubic centimeter can be given, but this concentrated suspension has caused incapacitating pain at the site of injection in some persons. If procaine penicillin G in oil and aluminum monostearate is used, Thomas advises 4,800,000 units given in divided doses of 1,200,000 units at intervals of two to seven days, or possibly it is preferable when given at intervals of two to four days. Quantitative serologic tests for syphilis are of great help in the follow-up of patients treated for early symptomatic syphilis. Seronegative primary cases may become seropositive immediately after therapy, but the tests should again be negative within a month after successful therapy. Seropositive primary and secondary cases should show definite drops in titers within six months after successful therapy. Complete seronegativity may not be obtained for a year or more, but as long as the drop in titers to low levels is maintained, re-treatment is unnecessary. Re-treatment is indicated when a rise of titers from previous levels occurs or when clinical relapse is evidenced by lesions of the skin or mucous membranes. In the absence of clinical relapse, a single rise in titers from previous levels should always be confirmed by repeated tests. Relapse or reinfection is associated with rapid and marked increases in titers.

Treatment of Early Forms of Syphilis.—After administration of 3,400,000 units of penicillin alone to 184 patients with early syphilis, Smelov,[117] from the Soviet Union, reports 3.7% relapses in primary seronegative syphilis, 5.5% in primary seropositive, 18.6% in early secondary, and 34.8% in secondary recidive syphilis. He quotes Studnicin, also of the Soviet Union, who in 1954 found penicillin alone "of no avail" in 7.2% of patients with early syphilis and failure after penicillin in 14%. In view of these findings, Smelov recommends one to five intermittent courses of treatment with penicillin, arsenicals, and bismuth, the number of courses depending on the diagnosis and the clinical course during treatment, and

supplemental fever therapy in "resistant syphilis." Emphasis is also placed on sufficient sleep, fresh air, exercise, good nutrition, and polyvitamin therapy. One is tempted to agree with C. R. Rein (unpublished communication) that in Russia either syphilis or penicillin is different than it is here.

Experiments on Use of Hyperthermia in Treatment of Primary and Secondary Syphilis.—Hyperthermia was employed in the treatment of early primary and secondary syphilis, in combination with penicillin in 44 cases and with arsenic and bismuth in 67 cases by Khokhutin,[118] at the Tomsk Medical Institute. The patients had had no previous antisyphilitic treatment. To induce fever, TAB vaccine was injected intravenously, a course of five or six hyperthermic reactions, each lasting 5 to 10 hours and repeated every three to five days, being given. Penicillin was given intramuscularly in a dose of 40,000 units every three hours, to a total of 5,000,000 units. As a rule the combined treatment accelerated the disappearance of T. pallidum from eroded lesions and speeded up the regression of primary and secondary syphilides and enlarged lymph nodes. The serologic reactions also became negative more rapidly. The results were better when hyperthermia was combined with penicillin than when metallotherapy was used, two patients failing to respond to the former and five, to the latter. The maximum follow-up period was seven years, though the number of patients kept under observation was never large and diminished steadily, only six patients in the first group and three in the second being followed up for longer than five years. Two patients in the first group and ten patients in the second suffered a serologic and clinical relapse within 6 months of treatment, and one patient in the second group developed asymptomatic neurosyphilis 16 months after completing treatment. The incidence of therapeutic failure was 9% in the first group and 23.8% in the second.

Rate of Titer Drop After Adequate Penicillin Therapy of First Infections and Re-infections in Syphilis.—Levitan, Miller, and Cutler [119] compared the rate of decrease of Kahn titer in a group of patients treated for a first syphilitic infection with another group treated for reinfection. All patients had primary or secondary syphilis at the time of treatment of re-treatment, and duration of infection and height of serologic titer were similar. After adequate therapy, the rate of fall in titer is significantly more rapid for a first infection than for a reinfection. The authors believe that this difference is a reflection of the longer period of infection with T. pallidum in the reinfection group.

Treatment of Latent and Late Syphilis

In order to diagnose latent syphilis correctly, asymptomatic neurosyphilis must be ruled out by spinal fluid examination and cardiovascular syphilis by fluoroscopic examination or teleroentgenography. No good evidence exists that latent syphilis, early or late, requires more treatment than does secondary syphilis; therefore, Thomas [111] advises the same treatment schedules as he advised for secondary syphilis. When the diagnosis is doubtful, because of failure to obtain a spinal fluid examination or to rule out cardiovascular involvement, a single treatment with 2,400,000 units of benzathine penicillin G would probably be effective for most patients with asymptomatic neurosyphilis. When in doubt, a total dosage of 6,000,000 units of procaine penicillin G in oil and aluminum monostearate given in doses of 1,200,000 units at intervals of two to seven days should provide sufficient therapy for patients with asymptomatic involvement of the central nervous or cardiovascular systems. A noticeable and relatively rapid decline in serologic titers during the first six months after successful treatment can be expected when early latent syphilis has been present for less than one year. When the infection has been present for more than one year, prolonged persistence of seropositivity is the rule. Relatively high titers usually decline within one year after treatment, but occasionally it is impossible

to obtain low titers by any regimen of treatment. Treatment for the sole purpose of obtaining negative titers is usually futile. On the basis of spinal fluid examinations, Thomas states that total dosages of 6,000,000 to 10,000,000 units of procaine penicillin G in oil and aluminum monostearate are sufficient for over 90% of all types of neurosyphilis, including paralytic dementia and primary optic atrophy. This does not mean that symptoms caused by irreversible changes in nervous structures can be relieved or that far-advanced cases of primary optic atrophy may not progress to blindness. The time to treat syphilis is before such advanced pathological changes have occurred. By analogy with neurosyphilis, treatment with 6,000,000 to 10,000,000 units of this form of penicillin can be advised for all types of late symptomatic syphilis. Individual doses of 1,200,000 units may be given two or three times a week. No data are as yet available on the follow-up of significantly large series of patients treated for late symptomatic syphilis with benzathine penicillin G. If this preparation is used, it seems to Thomas to be advisable to give at least three treatments of 2,400,000 units at intervals of no more than seven days. The purpose of this therapy is to increase the concentration of penicillin within the body rather than to prolong the duration of treatment. As is true of late latent syphilis, treatment of late symptomatic syphilis is not followed in most patients by seronegativity within 10 or more years. Regardless of the kind, amount, and duration of therapy, 70% or more of large series of patients treated for late latent and late symptomatic syphilis have been seropositive 10 years after treatment. The best guide to the activity of neurosyphilis is serial spinal fluid examination performed at six-month intervals. Pleocytosis in association with positive specific tests for syphilis in the spinal fluid indicates disease activity. After treatment, cell count should be less than 4 per cubic millimeter within six months to a year; high total protein content of the spinal fluid at the time of treatment should decline within a similar period, but the total protein determination may not be within normal limits for a year or more. High titers of specific tests for syphilis in the spinal fluid at the time of treatment should show a decline within one year after therapy, but the tests generally do not become negative for years. Relapse of neurosyphilis is indicated by the reappearance of increased cell count and frequently by increases in the total protein and in quantitative specific tests for syphilis in the spinal fluid. Titers of the blood serologic tests may or may not increase in the presence of relapsing neurosyphilis.

Treatment of Cardiovascular Syphilis

Leonard and Smith [120] studied 374 patients with syphilitic aortic incompetence; 222 patients died, and 102 survived (fifty remained untraced). Of the entire series, 75% were alive after 1 year; 54%, after 5 years; 32%, after 10 years, and 14%, after 20 years. The mean survival of all those who died was 48 months from the date of diagnosis. Female and younger patients had a more favorable prognosis. Forty-nine patients were free of symptoms at the time of diagnosis; this group had a good prognosis, 84% being alive after five years. One hundred eighty patients had cardiac pain at diagnosis. It was commoner in females aged less than 50 and carried a relatively good prognosis. Forty-six per cent of the patients survived 5 years, and sixteen per cent survived 20 years. One hundred eleven patients had heart failure at diagnosis. It was commoner in males and older patients and carried a bad prognosis. Only 15% of the patients survived five years. The diastolic blood pressure was a good index of prognosis. In untreated patients the E. S. R. was raised in 80% of those without congestive heart failure and in 64% with congestive heart failure. Calcification of the ascending aorta was noted in 35% of 64 cases. It was commoner in elderly patients. Many of the patients treated with penicillin are still alive. Although there

was no evidence that patients treated with penicillin and either arsenic or bismuth had a better prognosis than patients fully treated with either arsenic or bismuth alone, the provisional conclusion was reached that patients treated with penicillin alone appeared to have a slightly poorer prognosis.

Surgical Treatment of Aortic Aneurysms.—Cooley et al.[121] reported that of 253 patients subjected to excisional therapy for aortic aneurysms during the past five years, 185 had lesions of the abdominal and 68, of the thoracic aorta. Death occurred within the first weeks of operation in 24 of the former and 23 of the latter, with a total hospital mortality rate of 18%. The fact that virtually all of the 206 patients surviving operation were relieved of all symptoms and returned to a relatively normal life indicates that excisional therapy is the most effective method in aortic aneurysm.

Treatment of Neurosyphilis

The value of the treatment of neurosyphilis is coming to fuller realization as a result of important evaluation studies appearing during this period. Chief among these is the report by the American Cooperative Study.[122,123] A short review covering serologic tests, biologically false-positive reactions, TPI test, congenital syphilis, and treatment was presented by Timberlake[124] as his part of a comprehensive review of psychiatric progress in 1956.

Penicillin in Dementia Paralytica.—Borges Fortes[125] states that he treated three groups of 30 patients with dementia paralytica. The patients of the first group were given malariotherapy followed by penicillin and showed an improvement rate of 50%. Those of the second group were given 1,000,000 units of procaine penicillin G daily for 10 days and showed the same rate of improvement. Those of the third group received 2,400,000 units of benzathine penicillin G on the first, fifth, and ninth days, plus 500,000 units of potassium penicillin G every 12 hours, or a total of 17,200,000 units, in 10 days. This schedule gave an improvement rate of 83.3% and significant improvement in the serologic and spinal fluid findings. The patients treated with penicillin shortly after the diagnosis was established showed appreciable improvement, becoming quieter, less delirious, and less agitated. Their body weight also increased. The author believes that treatment with penicillin is superior to malariotherapy and that the relative efficacy of the different forms of penicillin should be evaluated.

Progression of Asymptomatic to Symptomatic Neurosyphilis After Penicillin Therapy.—Several authorities[122] reported the results of a cooperative study to determine the outcome of penicillin therapy for asymptomatic central nervous system syphilis and clinical, serologic, and spinal fluid studies. This report deals with the characteristics of patients with asymptomatic central nervous system syphilis and with the probability of progression to symptomatic neurosyphilis following treatment with penicillin. Within the seven-year observation period of this study, it appears that penicillin alone is capable of completely curing asymptomatic central nervous system syphilis; a total of 765 patients, 264 of whom had had no previous treatment, made up the study group. The findings indicated that the maximum cumulative probability of progression to symptomatic neurosyphilis following penicillin therapy is 0.55% at the first year, 1.69% at the third year, 2.02% at the fifth year, and 3.31% at the seventh year after treatment. Only 12 of the 765 patients treated were recorded as having shown progression of asymptomatic neurosyphilis at the last observation period. Of these patients, only one was unequivocally a treatment failure; the patient responded satisfactorily to re-treatment with a larger dose of penicillin. In the other patients there was no clear-cut evidence that the so-called progression did in fact represent progress of the disease process. It is probable that what was considered as progression represents manifestation at the level of clinical recognition of preexisting subclinical neuraxis damage.

The same authorities [123] reported the results of their cooperative study to evaluate the efficacy of treatment in 765 patients with asymptomatic neurosyphilis as measured by laboratory methods. In order to analyze changes in laboratory findings from all clinics as a single group of patients, it was necessary to consider test results as essentially unchanged, less positive, or more positive. They consider the range of cell count of 5 to 10 and total protein of 40 to 50 mg. per 100 cc. as a borderline zone and probably within the limits of normality. At most, from cell count studies it would seem that 9% of patients might be expected to show need for re-treatment at the end of one year's observation, without regard to the original penicillin dosage used. It is probable that this may exemplify a composite group of patients truly representing failure and patients slow to respond. The study would lead one to believe that persistently abnormal spinal fluid total protein levels alone are not, in themselves, indicative of poor prognosis. Spinal fluid tests for syphilis showed a gradual decrease in positivity with passage of time after treatment. The improvement in spinal fluid for syphilis is more rapid in the younger patient, in the one with disease of shorter duration, and in the one with abnormal cell count. Since 28% of their patients with asymptomatic CNS syphilis had a blood serologic titer of 2 units or less, a weak serologic reaction can not be considered as indicating absence of spinal fluid involvement. Following penicillin treatment for asymptomatic CNS syphilis there is a gradual trend toward seroreversal. However, changes in the blood STS following penicillin treatment do not reflect, with any degree of accuracy, changes in the spinal fluid test for syphilis. In the past, there has been speculation regarding the relationship of the response of blood titer and spinal fluid test for syphilis following penicillin treatment. Specifically, the question has been this: Is a blood titer decrease or increase after treatment indicative of a similar change in the spinal fluid test for syphilis? Of those with satisfactory serologic status (those who remained negative, became negative, or experienced a quantitative decrease of at least two dilutions) at three months after treatment, only slightly more than 20%, one patient out of five, showed a satisfactory spinal fluid test for syphilis status. At one year after treatment, approximately 60% of those with satisfactory serologic status also had satisfactory spinal fluid response, and this percentage did not increase materially at two years after treatment. On the other hand, among those with unchanged blood status at three months after treatment, 8.5% of the patients showed improved spinal fluid status, and at two years after treatment, 42% had experienced improvement in spinal fluid status. Lastly, among those who showed an actual increase in serologic titer at one year after treatment, 40% had satisfactory spinal fluid response. There seemed to be no relationship between serologic negativity and the degree of spinal fluid positivity at the onset of study treatment. Of the 765 patients diagnosed as having asymptomatic CNS syphilis, 32 (4.2%) were reported as being seronegative at this particular time in the course of the disease. Asymptomatic CNS syphilis responds extremely well to treatment with penicillin. Re-treatment on the basis of persistent positive laboratory findings alone is not recommended unless the cell count increases significantly after therapy, remains unchanged at an elevated level for six months after treatment, or increases significantly after approaching normalcy or near normalcy following treatment.

Results of Five Years of Penicillin Treatment of Neurosyphilis.—Orbán and Lazarovits,[126] from the University of Budapest, report the results of treatment of 254 patients with neurosyphilis during the five-year period 1949 to 1954. Of these patients 56 (22%) had meningovascular syphilis, 74 (29%), asymptomatic neurosyphilis or pupillary abnormalities only; 60 (24%), dementia paralytica or taboparesis, and 64

(25%), tabes dorsalis. Examination of the cerebrospinal fluid was performed yearly up to 1953 and afterward at six-month intervals. In 189 cases treatment was with penicillin alone, and in 65, with penicillin and fever therapy. During 1949 penicillin was given in courses to a total dose of 3 to 4.8 megaunits each, but after that date this was increased to 6 to 9 megaunits. Most of the patients appear to have received more than one course of penicillin. As a result of their experience the authors suggest the following doses of penicillin for treatment of neurosyphilis: In late asymptomatic and meningovascular neurosyphilis, 6 to 12 megaunits, and in dementia paralytica and tabes dorsalis, 12 to 20 megaunits. Fever therapy is recommended in cases where penicillin does not produce clinical improvement or in which the CSF does not return to normal after a reasonable period. Fever therapy is further recommended in cases of dementia paralytica, taboparesis, and progressive optic atrophy.

Late Results of Fever Therapy in Neurosyphilis.—Kopp and Raaschou-Nielsen [127] subjected 277 patients with neurosyphilis to a follow-up examination in 1954 and 1955. The patients constitute 96.2% of the 286 patients who were admitted for treatment during the years 1937 to 1952. More than one-half of the patients suffered from parenchymatous neurosyphilis. The observation period was 10 years or more for 70% of the group; 95% of the patients were observed for 5 years or more. One hundred eighty-three patients received treatment with fever, in most instances given as injections of colivaccine or with hypertherm; sixty-seven patients were given combined treatment with fever and penicillin. A small group, of 27 patients, received penicillin alone. Re-treatment was performed according to an over-all evaluation of the humoral, clinical, and social aspects of the patients. It was instituted as fever therapy, penicillin, or a combination of both in 30, 47, and 18 patients, respectively. The results of treatment were evaluated from humoral, clinical, and social points of view. Combined treatment was not found to be superior to treatment with fever alone. Treatment results are summarized as follows: 42.4% of all patients in the fever and combined treatment groups were improved or without symptoms at the follow-up; 66% of the surviving patients in the two treatment groups had full working capacities. Spinal fluids were examined with at least a six-month interval in 158 patients; 88% had inactive spinal fluids after treatment. The results of treatment within the diagnostic group are mentioned. The effect of treatment on certain tabetic symptoms and on the neurologic symptoms of congenital syphilis was inconspicuous. In 11 of 18 patients with optic nerve atrophy, progression of visual disturbances appeared to have been stopped. Recurrences were seen only in patients with severe neurosyphilis. They did not appear to be connected with the number of fever attacks with temperatures reaching 40 C (104 F). They were not seen in patients receiving physically induced fever. Concomitant therapy with arsenic and bismuth did not guarantee durability of the negativity achieved in serum or spinal fluid. Sixty-five patients died before the follow-up, but 77% of these had died for reasons other than neurosyphilis. The direct treatment mortality due to fever therapy was 2%. The duration of symptoms before treatment was found to be a valuable prognostic factor, whether the treatment results were compared on the basis of the clinical condition or the working capacity.

Treatment of Syphilis in Pregnancy and Congenital Syphilis

Treatment of Syphilis in Pregnancy.—Thomas [111] states that syphilis in pregnant women requires no more or different therapy than in nonpregnant women. The question continues to arise as to whether the woman who has acquired syphilis should be treated in each succeeding pregnancy. In general, available data indicate that this is unnecessary, provided the woman has received previous penicillin therapy with no subsequent

evidence of relapse or reinfection. When there is doubt about the adequacy of previous therapy, a single treatment with 2,400,000 units of benzathine penicillin G or four injections of 1,200,000 units of procaine penicillin G in oil and aluminum monostearate should be given during pregnancy. When syphilis is discovered very late in pregnancy, it is always advisable to treat it as soon as possible. Even when treatment is given only a few days before delivery, the fetus may benefit by the therapy, since penicillin crosses the placenta to the fetus.

Treatment of Congenital Syphilis.—Thomas [111] prescribes the same treatment in congenital syphilis as in acquired syphilis, except that he uses smaller doses in children weighing under 32 kg. (70 lb.). Infants and children should receive total doses of 75,000 to 100,000 units of penicillin per kilogram of weight. Procaine penicillin G in oil and aluminum monostearate in doses of 0.5 to 1 cc. (150,000 to 300,000 units) may be injected every two to four days until the total dosage is completed.

Herxheimer Reaction

Herxheimer Reaction in Early Congenital Syphilis.—Holzel [128] reports that during a five-year period, 1948 through 1952, eighty cases of congenital syphilis in infants and children were treated in three Manchester, England, hospitals. Mortality was 44% in those treated under the age of 3 months, 38% in those 3 to 12 months old, and 0 in those 1 to 14 years of age. Nineteen infants under one year died. Holzel believes that in 10 of these a Jarisch-Herxheimer reaction to penicillin was a contributing factor to death. In 3 of these 10 cases death occurred within the first 24 hours after the beginning of treatment. In these infants, there was a sudden rise in temperature, abdominal distention, extreme respiratory distress, and "a large vomit" preceding a final syncopal attack. In the other seven infants in whom a Herxheimer reaction was considered to have contributed to death, there was initial pyrexia, weight loss, abdominal distention, pallor, and diarrhea. Near the end of the first week after the beginning of treatment, death occurred with the picture of sudden peripheral circulatory failure. Most of these infants had hepatomegaly on admission. Thymol turbidity tests were grossly abnormal in all infants with florid syphilis, and Holzel states that the additional burden of a Herxheimer reaction in livers with severe parenchymatous damage due to syphilis may well have led to complete failure of hepatic function. Prevention of Herxheimer reactions by initiating treatment with very small doses of penicillin (100 to 500 units) and by oral administration in dosage of 100,000 units per kilogram of body weight per day for two weeks or longer is discussed. This is a scholarly paper, and the author's conclusions and recommendations should be given serious consideration by those treating early congenital syphilis.

Toxic Reactions to Penicillin

Reactions to penicillin are still the subject of considerable investigation. Besides a general review by Shoemaker,[129] Björnberg and Selstam [130] describe an acute psychotic reaction after injection of procaine penicillin and anaphylactoid reactions have been encountered by Maganzini [131] and by Nudelman.[132] A significant study by Babione [133] indicates that there was 59% decline in admissions to the sick list due to reactions to antibiotics in the Navy and Marine Corps from 1951 to 1955. Ninety-seven per cent of reported reactions to antibiotics were reactions to penicillin in 1953, 1954, and 1955. Though Naval strength rose and fell during the five-year period, there was a decline in reaction rates from 231 to 97 per 100,000 men per year, or 58%, from 1951 to 1955. This drop in reaction rates was sharpest from 1951 to 1953 and appears to be leveling off. The drop in reaction rates almost exactly parallels a drop in issue rates of injectable penicillin (all forms) and bears no demonstrable relation to changes in usage of oral penicillin. Since depot issue rates usually reflect the preceding three months'

usage rates, a figure of 1.8 reactions (lasting more than one day on the sick list) per 1,000,000,000 units of injectable penicillin as used in the Navy is suggested as a fair approximation to the facts. There were no deaths in the four years from 1951 to 1954, but two deaths occurred in 1955 after administration of intramuscular penicillin.

Syphiloid Diseases

The battle against the treponematoses continues and as in the past is largely stimulated and supported by the World Health Organization. The following reports speak for the massive and effective programs now in operation.

Comparative Studies on Histopathology of Syphilis, Yaws, and Pinta.—Hasselmann [134] states that lesions of primary and secondary syphilis present pronounced inflammatory changes in the intima and media of the capillaries, whereas such changes are always absent in pinta and occur in yaws only in the late stages when sudden necrosis with ulceration sets in as a sensitization phenomenon. He correlates this "mesodermotropism" or "panblastotropism" of the T. pallidum and the "epidermiotropism" of T. pertenue and T. pintae with the clinical manifestations of these three diseases, using as examples the early necrosis and ulceration of the primary lesion of syphilis and the occurrence of cardiovascular, central nervous system, and congenital syphilis and the absence of these manifestations in yaws and pinta.

Report of Second International Conference on Control of Yaws.—The Second International Conference on Control of Yaws, held in Nigeria, in 1955,[135] is a subject of a detailed report in the *Journal of Tropical Medicine and Hygiene*. Plans for the campaign and the latest developments in policies and techniques were thoroughly dealt with by the 53 participants from 30 countries. This report is a full summary of the papers and discussions at the conference and of the more important and recent writings bearing on the subject. It will furnish all those interested in yaws eradication with a useful compendium of the position at the end of 1955 and will put them in touch with sources of more detailed information.

Control of Yaws.—Hackett [136] points out that the control of yaws and its eradication is at present based upon mass treatment campaigns in which the whole population is surveyed and a single injection of a long-acting penicillin preparation is used. In addition to active cases of yaws, some policy must be followed in which that very important section of the community grouped under "latent cases and contacts" also receives protective treatment. Modern campaigns are based on clinical inspection and treatment carried out by trained auxiliaries of the country, or even district, in which the campaign is in progress, under adequate supervision. Resurveys at 6 to 12 months, in a simple manner, are essential and should continue until surveillance can be undertaken from established rural health centers. Such continued surveillance is an essential step in the eradication of the disease. The dosage of procaine Penicillin G in oil with 2% aluminum monostearate (PAM) recommended is 1.2 megaunits (4 ml.) for active cases of 15 years of age and older and 0.6 megaunits (2 ml.) for those under that age. Preventive doses for latent cases and contacts are half these amounts. A single intramuscular injection is given at the time of diagnosis. At present it is not recommended that benzathine penicillin replace PAM in mass campaigns against yaws. Much of the work of mass treatment campaigns must, because of the circumstances in underdeveloped countries where yaws is endemic, be carried out by suitably trained auxiliaries. Under adequate supervision their work can be very satisfactory. The areas of a yaws campaign should be regularly expanded from villages to districts and provinces, so that a compact zone is formed until the whole country is covered. In this way, reintroduction of infection by migrants is reduced. Similarly, coordinated action between countries should follow until large

and even continental areas are protected. With the campaign, and after it, in addition to the development of rural health centers, efforts should be directed to the improvement of the environment of the people, so that the transmission of yaws and other communicable diseases is no longer possible. To this end also the willing and understanding cooperation of the people is essential and must be earned at all stages in the control of yaws. In another report, Hackett and Guthe [137] indicate that the eradication of yaws could be brought about by the removal of the conditions that favor its transmission. To await this happy state would mean many years of delay. Since the only sources of infection are the patients with infectious lesions and persons likely to develop infectious lesions, the introduction of low-costing, long-acting procaine penicillin G in 2% aluminum monostearate (PAM) has made possible the earlier eradication of yaws. Important points in contemplating a yaws campaign in any endemic area are that much that is effective can be done at relatively little cost, with use of relatively simple techniques; that international assistance is available, if desired, and that populations who have been rid of yaws by properly conducted campaigns are often awakened to the possibilities of modern public health, the development of which is thereby encouraged.

Indonesian Treponematoses Control Project.—The Indonesian yaws campaign,[138] concerned as it is with a large part of the population of the republic of nearly 80,000,000, is the largest single yaws campaign in the world. It started in 1950 and, as in other of these early campaigns, several methods were tried before one was found that suited the conditions in the field. The importance of health education, surveillance in which very comprehensive action is taken, and the development of both curative and preventive services in rural areas is well recognized in Indonesia and is taking place about the subdistrict polyclinic. In Indonesia, the polyclinics in the subdistricts have been an essential part of the health services for many years. The yaws campaign is part of the duties of the polyclinic staff. Although only patients are treated in the campaign and the fall in prevalence is slower than if total mass treatment had been carried out, it is nevertheless, progressive, and with the admirable plans of the Indonesian ministry of health there is no reason, under existing conditions, why eradication of yaws should not be achieved as in other yaws campaigns.

Treponematosis Eradication, with Special Reference to Yaws Eradication in Haiti.—The campaign against yaws in Haiti [139] started in 1950 and was one of the first national campaigns to receive international assistance from WHO of technical advice and staff and from UNICEF of penicillin, equipment, vehicles, etc. The declared intention of this campaign is the eradication of yaws, by which is meant "a complete disappearance of all infectious cases from a country and the non-appearance of any primary autochthonous cases after the intensive campaign efforts have been terminated; in other words, the complete interruption of transmission." The difference between "control," whose objective is said to be "to reduce morbidity," and "eradication" is discussed, and the present practicability and need for eradication is stressed. Many of the eradication techniques have been developed from the Aedes aegypti eradication campaigns.

Analysis of Results of Treatment of Yaws with Single Injection of PAM.—In the extensive yaws eradication campaign in Haiti since 1950, material from a special clinic was set up in Bainet to evaluate the results of single injection of PAM in various dosages. Hume and Facio [140] concluded that a schedule of 600,000 units in a single dose is the treatment method of choice for mass campaigns against yaws, being highly satisfactory in both the primary and secondary stages of the disease, provided the PAM conforms to certain minimum standards.

Re-treatment does not follow the rules employed in the case of syphilis patients.

Yaws Eradication Campaign in Nsukka Division, Eastern Nigeria.—Zahra [141] also writes about yaws eradication. This is the outstanding yaws eradication campaign at present in Africa. It started in September, 1953, and the national government has received assistance from WHO and UNICEF. This successful campaign is an admirable example of all-around cooperation between the government, the field staff, the people, and international organizations. The further development of the rural health scheme should be watched with interest.

Endemic Syphilis in Bakwena Reserve of Bechuanaland Protectorate.—Murray and his colleagues [142] report in a beautifully illustrated article on a mass examination and treatment. The endemic infection is called locally, "dichuchwa." It is similar to bejel, njovera, and the endemic syphilis reported elsewhere in the world. It is a childhood and family disease and not spread venereally. Penicillin is effective therapy of it. Mass treatment of cases and contacts combined with an improvement in the standards of hygiene could eradicate the disease.

Endemic Syphilis and Yaws.—Grin [143] concluded from his studies that endemic syphilis and yaws are very similar and that any differences between them are not necessarily qualitative but may result mainly from environmental factors which over the course of years have been predominant in the various areas in which these infections are found. Because of the similarities of yaws and endemic syphilis, the measures for controlling endemic syphilis and analogous conditions, such as yaws, can follow the same or similar principles.

The "Unitarian Concept" of Treponemal Diseases.—According to Moschella,[144] the question whether all treponematoses are clinical entities or syndromes still remains speculative and provocative. Although the treponemes appear morphologically indistinguishable under the electron microscope, there has not been demonstrated sufficient biologic, immunologic, or experimental evidence to warrant acceptance of the "unitarian concept." Where bejel is endemic, the unitarian concept is most acceptable; where pinta is endemic, the concept is least accepted, and where yaws is endemic, there are mixed reactions.

Pinta in Mexico.—The geographic distribution and the epidemiology of pinta in Mexico is discussed by Marquez, Rein, and Arias.[145] In a group of 133 patients studied, 61.6% were between 1 and 15 years of age, with a further 28.6% being 16 to 26 years of age. The transmission of pinta is reviewed, and the possibility of insect vectors is rejected, except in rare instances. A review of the bacteriology of T. carateum is presented. The literature on the serologic results obtained in pinta is reviewed also, and Rein-Bossak test results of Beerman (1943) are tabulated. Nelson is quoted as stating that it has not been possible so far to differentiate T. pallidum from T. carateum by means of the TPI procedures. The clinical characteristics of pinta are presented in detail and are depicted. Results of treatment of pinta with PAM and Panbiotic (containing, in a single dose of 2 cc., in aqueous suspension, 300,000 units of potassium penicillin G, 300,000 units of procaine penicillin G, and 600,000 units of benzathine penicillin G [N,N'-dibenzylethylenediamine dipenicillin G]) in series of 665 and of 92 cases, respectively, are presented, (Rein et al.: *J. Invest. Dermat.*, 1953).

Control of Syphilis

In spite of reduced budgets and lessened interest, specifically in syphilis, much epidemiologic work is being pursued both in this country and on a world-wide scale. Although syphilis investigation has become part of a generalized program, case-finding both by examination of persons and their blood is yielding fruit.

Correcting Reported Incidence of Congenital Syphilis in Philadelphia.—Ingraham and Burke,[146] using as material 2916 cases of congenital syphilis, reported as occurring

in Philadelphia over a 26-year period from 1930 to 1955, demonstrate that crude morbidity reporting of congenital syphilis tends to reflect the extent of case-finding activity and is grossly misleading if used to evaluate effectiveness of treatment to reduce the occurrence of new cases. Referring reported cases of congenital syphilis to the year of their occurrence (the year of birth) provides a more accurate perspective of past performance and relation to current conditions. Of the indexes of syphilis control which may be applied on a current basis to test total program effectiveness, mortality from infantile congenital syphilis seems to align itself closest with the program changes. The universal use of penicillin to treat the syphilitic pregnant woman has created additional problems in correcting infant morbidity statistics for congenital syphilis because of the growing tendency to treat all seropositive infants and the feeling that infants, if treated, must be considered syphilitic for purposes of record-keeping and subsequent follow-up.

Venereal Disease Contact Interviewing.—Peevey,[147] in discussing the venereal disease contact interview, states that two factors are especially detrimental to successful contact interviewing: 1. Uninformed interviewers have an inclination to limit efforts to one report per person. 2. Patients who have had multiple contacts are inclined to disclose only the one person they suppose caused the infection. Interviews are to be carried out in such a manner that the patient can be assured his interests will be protected and contact information will be restricted to official medical use. Speedy preparation and direct mailing of reports reduce betrayal risks and permit prompt action by investigating agencies.

Syphilis Follow-Up Program Among Veterans After World War II.—Taggart and his co-workers[148] reported that of the 500,000 veterans who either acquired or were treated for syphilis during the years 1940 to 1946, 122,000 met the following criteria to be included in this study: Their spinal fluid was doubtful or was positive when examined, or it was not examined, or treatment was inadequate. Since the Veterans' Administration was not permitted to conduct such an investigation, the venereal disease program of the United States Public Health Service was asked to do so. They began sending out report forms in December, 1949; follow-up began in January, 1950. Of 122,461 forms sent, 90,293 had been returned by January, 1953. Of those returned, 8578 forms contained only data already on file. Of the remaining 81,715, forty-five per cent could not be located, eleven per cent were located but not examined, and nine per cent either were in service, had died, or refused examination. Of the 27,786 who had serologic tests for syphilis during this follow-up, 18.8% were seroreactive; 2.7%, doubtful, and 78.5%, negative. A total of 13,837 spinal fluid examinations were performed, with 586 doubtful or positive results and the remainder negative. Of these spinal fluid reactors, 140 were detected for the first time during this survey. A comparison is made of the results in whites and in Negroes. It is predicted, from these findings, that approximately 3% of the 500,000 veterans, or 15,000 in all, will ultimately contract neurosyphilis. The use of penicillin and its effect on this outcome is discussed. Only syphilis case-finding programs will enable the detection of these latent cases and circumvent the need for long and costly hospitalization of these veterans.

Compulsory Blood Testing.—An editorial in *The Journal of the American Medical Association*[149] reports that according to a panel of eminent dermatologists and public health representatives, the legal requirements for premarital and prepartal serologic blood testing should not be rescinded until all the many questions for and against such legislation have been answered by a sound epidemiologic study. In general, it was the panel's unproved assumption that compulsory-blood-testing laws have contributed to the reduction of morbidity due to syphilis.

It was also believed that such laws brought many persons to necessary medical care who would never have sought it. However, careful epidemiologic studies, not theories, are needed to settle the value of compulsory blood test.

Contributions of Premarital and Prenatal Blood Testing in Syphilis Control.—Magnuson and his co-workers [150] feel that much is being accomplished in syphilis control through premarital and prenatal blood testing. It is estimated that through the effectiveness of prenatal blood testing, 1000 infant deaths from syphilis were prevented in 42 states during the first five years following enactment of the law. Conservative estimates indicate that 1200 to 1300 previously untreated syphilitic persons are found annually through premarital blood testing. By adding to these infections the previous contacts from which the initial infections were acquired, one case actually detected should be increased to perhaps five cases to measure more accurately the efficiency of premarital epidemiology and case-finding. Premarital and prepartal blood-testing legislation, when properly administered, contributes to venereal disease control by detecting and bringing or returning to treatment persons with syphilis, preventing the transmission of syphilis to marital partners, protecting unborn children from congenital infection, reducing morbidity and mortality due to syphilis and to other causes among infants by encouraging prepartal care, and providing opportunities for general health education. There remains much to be done toward the prevention and control of congenital syphilis. As long as cases of congenital syphilitic infection continue to be found in our population, there is a definite need for strict enforcement of blood-testing legislation.

Baltimore Multiple Screening Clinic.—Roberts, Wylie, and Glasser [151] summarize some of the major findings of the Baltimore Multiple Screening Clinic and suggest whether it was a success or a failure. The 2024 persons who attended the clinic were screened by electrocardiograms, blood-pressure readings, miniature chest x-rays, urine and blood-sugar tests, and serologic tests for syphilis, followed by a TPI test for checking (if positive) vision, hearing, and weight tests. Of 552 persons referred to physicians because of previously unknown abnormalities, 309 visited their physicians within six weeks of the clinic attendance. Physician cooperation was good. Only 53 persons were reactive to the serologic tests for syphilis; 14 of these 53 completed follow-up, which was confirmed by the physician in four instances. In only one instance, however, was the syphilis previously unknown to the physician. The cost of multiple screening is discussed; it is shown to be an expensive procedure. The screening tests for diabetes, heart disease, hypertension, anemia, diabetes, and tuberculosis had a fairly satisfactory performance. Those for proteinuria, syphilis, and "other chest" conditions gave unsatisfactory results. The Commission on Chronic Illness reports in a later study [152] results of a screening clinic of the Baltimore study of chronic illness, which was conducted to determine what multiple screening tests were most practical. This battery of tests included height and weight measurements, questionnaries for heart disease, six-lead electrocardiogram, blood pressure determination, visual and hearing acuity tests, miniature chest x-rays for tuberculosis, urine albumin test, urine and blood sugar tests, hemoglobin tests, and serologic tests for syphilis. All of these tests were completed within one hour. Of 7000 persons sent invitations to attend, 2024 (29%) responded. From the results of these tests, conducted on what is believed to be a representative section of the population of Baltimore, it is concluded that multiple screening is a procedure of promise. The serologic test for syphilis was found to be a useful procedure, yielding 53 positive instances, in most of which a TPI test was done.

Serology Control Program of Venereal Disease Research Laboratory.—Harris and

Bossak [153] report that the serology control program of the venereal disease research laboratory was evolved to assist state laboratories in attaining and maintaining a high level of efficiency in serologic testing. This program has nine integrated segments, which are providing a laboratory manual prepared by the staff of the Venereal Disease Research Laboratory; providing reference standard serologic reagents prepared by the staff of the venereal disease research laboratory; inspecting laboratory serology control programs; conducting scheduled training courses; conducting field refresher training courses or work shops; standardizing and supplying dehydrated control serum; conducting hemisphere-wide serologic evaluation studies on a continuing basis; participating as a control or co-control in intrastate serologic evaluation studies, and offering a T. pallidum immobilization (TPI) testing service, nation-wide, through the state and territorial laboratories. Concerning the TPI testing service, during the first month of 1956, requests for this service were at the rate of approximately 100 per week. According to Stout,[154] the field consultation services of the Venereal Disease Research Laboratory of the Public Health Service during a five-year period which includes the fiscal year 1956 have included reviewing the syphilis serology activities and programs of the state health department laboratories, assisting states in field refresher training courses or workshops in syphilis serology, and inspecting serologic testing in Public Health Service hospital and clinic facilities. Utilizing such services has aided state health department laboratories to develop state-wide programs for the standardization and control of syphilis serology.

Seropositive Syphilis.—According to a foreign letter in *The Journal of the American Medical Association,*[155] one of the functions of the serodiagnostic department of the Norwegian State Institute for National Health is the Rh-typing of blood of the husbands of Rh-negative pregnant women. In the course of such typing, the opportunity is taken to test the sample of blood for syphilis. Between Jan. 1, 1951, and July 16, 1955, a total of 16,489 samples were thus tested, and in 87 cases one of the serologic tests for syphilis was positive. In 64 of these cases there could be no doubt as to the diagnosis of syphilis, and J. Eng, who reports on this study in *Tidsskrift for den norske lægeforening* for June 15, concludes that about 0.44% of the subjects tested were syphilitic. Thirty of the sixty-four already knew they were syphilitic. The value of this study is enhanced by the facts that the sampling was random, in that the persons examined were not more likely to be infected with syphilis than any other group of married Norwegians, and that the samples came from all over Norway. As a result of his findings, Eng urges routine premarital examination for syphilis for both men and women, a precaution already in force in many countries.

Evaluation of Venereal Disease Control in Alabama.—Smith [156] discusses venereal disease control in Alabama from the year 1932 until 1956. In 1932 there were about 2000 cases of an inadequately reported epidemic and poor local facilities. Treatment centers went from 9 in 1932 to a high of 189 in 1942. Morbidity went up to 32,507 in 1945. Since 1945-1946, facilities have been reduced as morbidity statistics lessen. Smith says the picture is one in the round. It began with 2000 cases a year and has returned to 2000 cases a year. The return to local treatment in health departments completes the picture in the round. The fact that reduced facilities, reduced contact investigation, and reduced epidemiologic work-up are big factors in lower reported morbidity does not bother Smith at all.

Blood Tests for Syphilis in Connecticut. According to Hibbard and Benham,[157] the total number of blood specimens tested during 1955 in 84 laboratories in Connecticut was 387,291, as compared with 382,802 in 1954. The number examined in the laboratory service section of the Connecticut

State Department of Health decreased by 1484 below 1954; while there was a total increase of 5973 specimens examined in the other 83 laboratories in the state. These specimens are given in the following categories: premarital, prenatal, industrial, and "other diagnostic," with a total of only 10,623 reactive specimens among the 387,-291. These, particularly the "other diagnostic" category, include repeat specimens and biologic false-positives, and so the percentage of reactors, or 2.75%, does not indicate the true incidence of syphilis in Connecticut. For the respective categories, the figures read: premarital, total specimens, 36,014,355 reactors; prenatal, total specimens, 48,344,408 reactors; industrial, 45,-197,358 reactors. In these categories, the percentage of reactors was always less than 1%.

V. D. Survey in Virginia.—An appeal is made by Love and his group [158] to members of the Medical Society of Virginia to cooperate in the state-wide biostatistical survey of all known cases of venereal disease in Virginia during the month of July, 1956. The survey will be conducted by the Virginia State Health Department. It hopes to answer the question as to whether venereal disease is increasing or decreasing in Virginia and what its present status is.

Serologic Survey for Syphilis in Migratory Labor Camps of Upstate New York.—Thomas and Giordano [159] organized two teams which operated in camps located in eight counties of northwestern New York State. Of 5021 serologic tests for syphilis done on nonwhite migrants, 812, or 16.2%, had definitely positive results, and 322, or 6.4%, had doubtfully positive results. Histories of adequate previous treatment were obtained from 236 of the patients with positive or doubtfully positive tests. They treated a total of 770 patients for presumed syphilis. Their data show some past accomplishments, but the great majority (over 70%) of the reactors in the younger age groups had no treatment for syphilis. If syphilis is to be controlled, case-finding in the younger age group is essential.

Trend in Age of Acquiring Venereal Disease in New York City.—Rosenthal and Vandow,[160] in analyzing the new venereal disease infections reported to the New York City Health Department for the years 1944 through 1954 and comparing them with a similar analysis for the years 1940 through 1943, found that the decrease in median age for acquiring primary or secondary syphilis seen from 1940 to 1943 was reversed, so that by 1954 the median ages were practically the same for males and females as in 1940. Although the median ages for both males and females acquiring gonorrhea have gradually risen since 1944, they still remain slightly lower in 1954 than in 1940. There is an increase of 55% in the proportion of males in the 15- to 19-year age group who acquired primary and secondary syphilis in 1954 as compared to 1940. The proportion of females acquiring gonorrhea more than doubled in the 15- to 19-year age group, increasing from 8.8% in 1940 to 18.6% of the reported cases in 1954.

Syphilis Morbidity Reporting in Montana.—Clark and his co-workers [161] have found that the content and emphasis of a syphilis control program have a greater influence over the number of cases reported than does the rise and fall in the rate of infection, in the experience of the state of Montana. Increasing the State Board of Health field work and central office efforts materially increased the number of current cases reported. The decline in the number of cases of syphilis reported from all sources more nearly paralleled the trend in expenditures for venereal disease control by local and state health departments than it did the probable rate of infection.

Venereal Disease Morbidity Reporting by Private Physicians.—According to Ball,[162] the number of cases of venereal disease reported by the South Carolina State Board of Health has risen from 514 cases in the month of November, 1954, to 1678 cases in the month of May, 1956. A new reporting procedure for private physicians is described. This procedure, which took effect July 1, 1955, eliminates reporting by name.

The physicians, who were previously reluctant to reveal cases, now respond much better. During May, 1955, private physicians reported only 11 cases of syphilis, while in May, 1956, they reported 410 cases. In May, 1955, they reported only 12 cases of gonorrhea; in May, 1956, they reported 199 cases. Additional control measures are being instituted. It is emphasized that the fight against the veneral diseases is not yet won.

Epidemiology of Syphilis.—In another paper, Ball [163] reports that each case of syphilis is potentially the beginning of a widespread chain of infection. Striking examples of such spread are the two epidemiological chains uncovered this year by health department personnel in South Carolina during a two and one-half month period. An 18-year-old girl came to the Florence County Health Department with a rash typical of secondary syphilis. An interview revealed 22 contacts, of whom 19 were located in Florence and vicinity; 3 of these were found to be infected. A cluster survey in a section to which 85% of the contacts were traced led to the examination of 384 blood specimens. Eight new cases of syphilis were brought to treatment through these blood examinations. Another epidemiological chain of syphilitic infections was discovered in tracing the contacts of a 20-year-old youth with a penile lesion. Blood testing was then instituted in contact areas, and about 400 persons voluntarily accepted the blood-testing service. This included 200 students of the 10th to 12th grades in one school. The chains yielded 25 new cases of early syphilis. The records of the State Board of Health of South Carolina during the 12 months preceding this report revealed that 822 physicians submitted blood specimens for serologic test for syphilis, indicating that over 50% of the South Carolina physicians are still encountering syphilis in their practice. Private physicians are now seeing and reporting approximately 50 early cases of syphilis (primary or secondary) per month. Follow-up investigation of contacts of these private cases will not be instituted unless or until the physician himself makes such a request. The private physician is morally a public servant, just as the workers in organized health agencies are officially so. Public health agencies can assist by relieving him of at least part of this responsibility. The South Carolina State Board of Health is now offering to physicians an epidemiological service consisting of patient interview and contact investigation.

Venereal Diseases Campaign in Chile.—Coutts and his co-workers [164] state that in Chile PAM became available in 1948 for treatment of all patients with primary or secondary syphilis in a dosage of 3,000,000 units. Contacts and patients with dark-field negative genital lesions receive identical treatment. Two injections of aqueous crystalline penicillin are given for gonorrhea, since results with PAM were unsatisfactory. No penicillin-resistant gonococci have been found. All of the venereal diseases have shown a most satisfactory decline since 1947, but nongonococcal urethritis and vaginitis have rapidly increased in incidence and at present represent nearly 45% of those with genital discharges. Trichomonas vaginalis is the most commonly found pathogen. Antibiotics administered for causes other than venereal diseases are considered a factor in this decline; in a large group of nonvenereal patients over 60% had been treated for a nonvenereal cause with some antibiotic, principally penicillin.

Organization of Syphilis Control in Soviet Union.—Kozhewnikov,[165] of the Institute of Advanced Medical Studies for Physicians in Leningrad, outlines the measures used for syphilis control in the Soviet Union. Among these are obligatory registration, free treatment and examination, follow-up, epidemiologic work, prophylaxis, health education, and legal penalties for intentional contamination. Patients with primary or secondary syphilis are hospitalized within 24 hours after diagnosis and must remain in the hospital for 1½ months for

the first course of treatment, after which further therapy is administered at outpatient clinics. Mobile teams visit isolated clinics at weekly intervals. It is stated that oxophenarsine hydrochloride (Mapharsen) and so-called accelerated methods of treatment, which were widely used in the Soviet Union between 1944 and 1948, were followed by relapses in 10% to 17% of the cases and were abandoned! Penicillin is not mentioned. Early syphilis decreased markedly from the twenties until 1941, increased during the war years, and since then has shown a 19.4-fold decrease in the year 1955. Paresis and tabes have decreased one-hundred-fifty-fold, compared with prerevolution figures. Improvement of living conditions, elimination of unemployment and prostitution, steady growth of Soviet culture, a good system of mother and child welfare, and the functioning of the venereological institutes are all considered to have played important parts in this decline. The U. S. S. R. now looks forward to complete elimination of syphilis within the next few years.

Syphilis in Egypt.—Ruge [166] found that there was an average of 3% syphilis in a group of about 28,000 persons in a mass study in Egypt (Nile delta and a village in upper Egypt). Children had 1.2% and 1.4%; 16- 45-year-old group, 2.9% and 3.%; over 45-year-old group, 7.0% and 10.3%. Women had slightly more than men. He also commented on statistics from other centers. After an experience with 113,000* serologic studies, mostly with the combinations Wa.R./MKR in Tanta and MKR/VDRL in Cairo, and in Kiel by the Wa.R. (Kolmer with cardiolipin), Ruge [167] concluded that the combination MKR/-VDRL is very well proven. If one has clinical study and a Wa.R. (Kolmer) he may expect a trustworthy result of practically 100%. Hentsch,[168] too, evaluated the Wassermann and Kahn tests in the tropics.

Hong Kong Social Hygiene Service.—Doubling of the population in the period from 1946 to 1952, due largely to an influx of refugees, many of whom live as squatters in flimsy shacks; the presence of many Chinese men who leave their wives and families at home; periods of boom and depression which cause periodic unemployment; a large amount of shipping and a permanent sampan population estimated at 120,000, and the presence of naval and air units of the United States and Great Britain are factors in the high incidence of venereal disease in Hong Kong, according to Thomson.[169] Over 34,000 patients attended the government clinics each year in 1953, 1954, and 1955. Of these, 10,000 or more had gonorrhea; 2000 or more, chancroid; 200 or more, lymphogranuloma venereum; 4000 or more, syphilis, and 13,000 or more presented venereal disease. Prostitutes are invited to attend the clinics once a week for examination and in many cases are given, in accordance with a WHO recommendation, a weekly injection of penicillin. Attempts are made at epidemiologic investigation and at education.

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Progress in the Long-Term Management of Coronary Artery Disease

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The last decade has seen significant advances in our knowledge about atherosclerosis and treatment of coronary artery disease. Although we are still very far from the final answer, the clinical management is obliged to keep pace with intermediate progress. It is the purpose of this review to comment on the therapeutic implications of such progress made. Without going into the diagnostic approach for an early case of the insufficiency of coronary arterial system, we wish to deplore the lack of any significant advances in recent years in this field.

Regarding the general management of such patients, a few recent trends deserve mention, such as the importance of patient education about his disease and making a plan of treatment for the individual patient. Change of vocation should be considered with great conservatism and advised only where the work of the patient involves a type of circumstance that would precipitate anginal pain. Most physicians would allow moderate consumption of alcohol and minimum of tobacco. In cases where definite relation of anginal pain exists to smoking, complete abstinence is mandatory.

Weight Reduction

Postmortem studies of Bahr,[1] 1938, demonstrated relative paucity of atheromatous deposits in poorly nourished persons. Wilans,[2] 1947, similarly demonstrated resorption of arterial atheromatous deposits in people dying of chronic wasting diseases. This constituted an indirect evidence to implicate good nutrition or overnutrition with genesis of atherosclerosis. However, several subsequent autopsy studies by Moritz,[3] 1946; Yater,[4] 1948, and Faber,[5] 1949, have failed to discover any correlation between obesity and arteriosclerotic lesions in coronary arteries or aorta. Evidence for obese people having higher serum levels of cholesterol seems convincing. A significantly positive correlation between relative weight and serum cholesterol levels was reported by Mann and Stare,[7] 1954, quoting, in addition to their own, other independent studies. It should be mentioned, however, that predictable value of such raised levels of serum cholesterol for development of atherosclerosis rests today on very unfirm grounds, as we shall see later. Keyes and Anderson,[8] 1954, on the basis of broad population studies, concluded that influence of excessive caloric intake and obesity per se is small. In spite of the above controversial viewpoints, there is little to dispute that an overweight patient would reduce the work load on his heart by reducing his weight. In fact, a patient of so-called calculated normal weight will benefit by an attempt to reduce a few pounds, mainly to help regulate and moderate his dietary habits.

In the past, on the basis of the concepts above, a low-calorie diet was recommended for the victims of coronary artery disease. With studies such as the broad population studies in various countries of Keyes et al.,[8] 1954, mentioned earlier, relating the development of atherosclerosis closely to the total intake of fats rather than caloric intake, there sprang up the question of the ad-

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visability of a rigid restriction of fat intake in these patients. Severe restriction of fat in diet, apart from the possibility of hampering a balanced nutritional status,[7] is known to have made the subjects very irritable and short-tempered.[9] A great volume of work indeed is in progress in an attempt to elucidate the rationale of such restriction. However, so little has been uncovered that the confidence in the decision to institute it and recommend it to the patients today remains a personal one to every physician.

Fats and Atherosclerosis

Association of atherosclerosis with fats stems from the demonstration (Vogel, 1847, cited by Blumenthal [10]) of the presence of cholesterol in the atheromatous plaque. The origin of this deposit remains obscure till today. It resides in the realms of speculation to say whether atheromatous deposit is primarily initiated by changes in the arterial wall or comes from the components of the plasma.

In favor of the arterial wall theory stands an undeniable fact that atheromatous lesions are patchy in distribution. Further, these lesions have a predilection for areas that are under greater mechanical stress, for instance, just before bifurcation of the vessels. These lesions are also more frequent on areas previously scarred with rheumatic or syphilitic processes. Even in experimental animals with subintimal atheromatous deposits produced by feeding cholesterol, the typical medial lesion does not develop unless an injury is caused to the vessel wall.[11] Chernick [12] and associates, 1949, fed labeled acetate and phosphorus to rats and showed that the artery could incorporate these and synthesize phospholipid. Shore et al.,[13] 1954, working on experimentally produced atheromatous rabbit aorta, presented evidence that the rate of such synthesis was five times greater as compared to the normal rabbit aorta. Taylor,[14] 1950, and Waters,[15] 1954, have experimentally produced arterial lesions resembling somewhat the human disease by physical (freezing) and chemical irritation, yet the lipid deposition could not be demonstrated in these lesions under normal conditions, although this could be induced by producing hypercholesterolemia or filtering normal plasma under pressure. Localization of injected particulate matter has been shown to occur selectively at such areas. With injected lipid particles, "foam cell transformation" was demonstrable that masked the inflammatory character of this reaction and simulated early human arteriosclerotic lesions.

Lansing,[16] 1954, reported that although the amount of "elastin" in human aorta and pulmonary artery does not seem to change with age, yet its composition does so. It has been postulated that this change may be on account of diminution of an enzyme "elastase," which is an islet-cell pancreatic hormone with no digestive function but possibly a systemic one.

So little is known otherwise about the biochemical structure of normal and degenerating elastic tissue as well as the ground substance that the question of the origin of lipids in atheroma must remain a controversial one. In the present state of our ignorance, then, all possible factors deserve equal attention. The biochemistry and metabolism of the normal vessel wall and the multiple influences, such as mechanical hemodynamic, toxic, nutritional, and hormonal, to which the vessel wall is subjected need clarification.

Perhaps at the expense of our ignorance, the hypercholesterolemia theory has gained an impressive support and momentum. The concept runs as follows. Lehninger,[17] 1954, states that the vessel-wall intima and media differ markedly in lipid content and the intima has a lipid content practically identical to that of the plasma, even as regards free and esterified fractions of cholesterol. In the early atheromatous plaque, the ratio of the various lipids has been found to be the same. In later stages, however, the cholesterol increases in proportion. The reason for this increase is not known. Selective

removal of lipids other than cholesterol by phagocytes has been postulated. Further support for the exogenous source of cholesterol in the atheromatous plaque is obtained from isotope studies. Biggs and Kritchevsky,[18] 1951, fed tritium-labeled cholesterol to rabbits and demonstrated that the subintimal deposits thus produced in this animal derived their bulk of cholesterol from the plasma. However, such studies, including the similar ones mentioned previously to demonstrate the ability of arterial tissue to synthesize lipids, lose some of their significance in the light of the knowledge that great variations exist in different species as regards the regulation of cholesterol metabolism. The human organism displays a quality superior to that found in other organisms of keeping its cholesterol relatively constant in the blood.[11a]

The bulk of support for this theory has, however, come from the experimental studies. In its favor speaks the demonstration by Taylor and Waters that injury alone cannot produce an experimental atheromatous deposition while hypercholesteremia could, although a much greater similarity to the human lesion is obtained by the two together. Yet it is important to recognize the marked disparity between the human disease and its experimental production by hypercholesteremia alone. The human form, so different in distribution, is characterized by the degenerative changes in the entire vessel wall, and it is not settled whether lipid deposition is an early[16] or a late sequence.[10] In the experimental form the lipid deposits appear in the arteries and veins of all sizes after saturating the other organs in the animal bodies. The deposits occur in the intima of the vessels and are completely reversible. They further lack the changes in the elastic tissues and ground substance as well as thrombosis in the vasa vasorum, which is so typically seen in human atherosclerosis. The above distribution of lipid deposits in the experimental animal in fact finds a greater resemblance to the one in some hyperlipemic states in humans other than atherosclerosis, such as familial hyperlipemia and hypothyroidism.[10] While evaluating the vast experimental data on relation of lipid metabolism to arteriosclerosis, it is important to remember that one is viewing it through the tinted glasses of the above discrepancy.

Gould,[11] 1954, summarized the concept recognizing the importance of both local and systemic factors in production of the atherosclerotic lesion. While the former would be responsible for distribution and localization of the lesions and hence determine the prognosis, the systemic factors, on the other hand, should lend themselves to the general preventive measures.

Significance of Disturbed Serum Lipid Components

Association of lipids with atherosclerosis has stimulated much interest in the study of their metabolism in health and disease. Recent isotope studies[19] have disclosed that after absorption from the intestine there is a random rearrangement of fatty acids in various lipid components and resynthesis of glycerin. The long-chain fatty acids maintain their identity and go through the lymph directly to the blood, while short-chain acids are sent to the portal circulation and metabolized through the liver.

In the serum in the state of health the total cholesterol concentration as well as the ratio of the free and esterified fractions (the latter depending upon a healthy liver) maintain a remarkable constancy. Also, for the same person, the serum lipid phosphorus keeps a constant relation to the total cholesterol, yet when any variation does occur in the free component of cholesterol, lipid phosphorous also changes accordingly but the rate of this change is not a constant. Hence, any change in the lipid phosphorus is a reflection of a change of the amount of free cholesterol in relation to the esterified fraction and has no more independent significance.[20] Gertler et al.[21] 1950, reported cholesterol-phospholipid ratio to be significantly higher in patients with known

coronary artery disease as compared with controls. The main rise of blood cholesterol was noted to be in the esterified fraction as expected. The authors postulated that on account of the effect of phospholipids on the solubility of fats their decrease may produce an alteration in the colloidal make-up of lipids. Paterson et al.[22] 1956, in a scrutinizing study correlating the antemortem lipid determinations with the degree of atherosclerosis assessed at 50 autopsy examinations, reported a relative decrease of phospholipid as compared to the total cholesterol. Lindqvist and Isaksson,[23] 1956, in their experiments on severe dietary restriction of fats, noted a decrease in phospholipids, mainly comprising the nonlecithin fraction. Hence, they suggest that the ratio of total cholesterol to lecithin, rather than phospholipid, is a more vivid index of change.

Because of the above property of constancy of level and relative ease of determination, total cholesterol has been erroneously taken as a parameter of whole lipid metabolism.

Morrison and associates,[24] 1948, and Gertler et al.,[21] 1950, have presented evidence that patients who have suffered from coronary thrombosis display higher levels of serum cholesterol as compared to the so-called controls. Contrary opinions are available.[20] Lewis et al.[25] 1956, in a cooperative study on lipoproteins and atherosclerosis, conclude that appearance of clinical manifestations of atherosclerosis is associated with prior elevation of the total serum cholesterol, although such elevation cannot be used to predict the occurrence of clinical episodes. Bjork and associates,[26] 1957, find a significant difference between serum cholesterol of patients who have had myocardial infarctions and the controls so long as their age group fell between 40 and 49 years. In the higher age group this difference was obliterated. The explanation of how raised cholesterol could promote atherosclerosis is entirely conjectural. The incomplete knowledge of the regulation of plasma cholesterol level provides ground for some speculation.

Although there are no species differences in the cholesterol contents of tissues in animals, the level in the blood is species-specific. A very rapid exchange keeps on occurring between the free cholesterol in the plasma and in the liver. In the liver the esterified fraction has to increase first before an increase in the serum cholesterol can occur. In fact, this increase in the liver is mentioned as the most sensitive index of increase in the amount of total cholesterol in the body.[11a] Cholesterol synthesis in the liver is quickly influenced by external stimuli. It is markedly depressed by providing the body with exogenous cholesterol, as shown by liver-slice technique[27] and confirmed by isotope studies.[28] In the case of biliary obstruction it has been shown that both the serum level and the rate of synthesis in the liver are elevated. That this is due to retention of bile salts is shown by the fact that intravenous injection of other surface-active agents (Triton WR-1339) cause the same effect.[29] It is postulated that these agents probably act as binding agents for cholesterol and hence act as stimuli for more production.[29] Gould,[11a] 1954, postulates that α- and β-globulins in the plasma may be acting as such binding agents in a lipoprotein molecule and by providing excess of combination sites for cholesterol may be acting as a stimulus for its greater production. The break-down of such lipoprotein molecules caused by the abnormal processes in the arterial wall may lead the way to formation of an atheromatous deposit. By the experimental administration of surface-active agents to rabbits, it has been shown first, that they prevent atheroma formation, and later, on prolonged administration, actually accelerate it.[30] Hirsch and his coworkers have introduced a concept that the fatty acids that are liquid at body temperature (oleic and linoleic acids) act as solvents for cholesterol and other lipids which are solid at body temperature. It is conceivable

that the local nonavailability of these fatty acids may help deposition of cholesterol.

Since the amount of free lipids [32] in the plasma is extremely small, the lipids in the plasma and lymph are carried chiefly in combined forms. Very large particles called chylomicrons appear postabsorptively and are quickly removed in a state of health by the tissues. These are very rich in triglycerides, and their detailed structure is unknown. These are responsible for alimentary lipemia and perhaps for pathological lactescence.

In order for the serum lipids to carry on their metabolic functions in aqueous environments of the tissues, they are carried as protein-bound marcromolecules, known as lipoproteins. These are loose combinations, because they can be extracted from proteins at low temperatures, yet highly specific, as they cannot be easily resolved by mechanical forces. Their exact nature is also unknown. They can be separated by electrophoresis or by ultracentrifuge into two main classes. Low-density β_1-lipoproteins contain 25% globulin by weight and varying amounts of cholesterol, phospholipids, and triglycerides. The cholesterol content in these exceeds the phospholipids, and the triglycerides increase in the spectrum, with progressively lowering densities and rising flotation rates. Alpha-lipoproteins contain relatively more protein and less lipid and also have more phospholipids as compared to the cholesterol.[20] They have a higher density and lower flotation rate on the ultracentrifuge. Normal ratio of β- to α-lipoproteins is approximately 2:1.

Seventy per cent of the plasma sterols are normally carried in β-lipoproteins, and even more so in pathological states. Evidence is available that these are higher in men as compared to women, in the aged as compared to the young, and in atherosclerotic patients.[33] Normally,[32] there is a constant tendency in the body for the very low density lipoproteins to be degraded in the direction of normal β-lipoproteins. This is done by an enzyme contained in the tissues that has been called the "clearing factor," which attacks the triglycerides of chylomicrons and lipoprotein, in distinction to the intestinal lipase, which can only attack the non-protein-bound triglyceride. Heparin acts as a prosthetic group of this enzyme, and the presence of albumin or divalent salts such as calcium facilitate the reaction by acting as fatty-acid acceptors. The role and nature of α-lipoproteins are less known. Anfinsen,[19] 1955, suggests that they activate the triglycerides in some way for the action of heparin. Transiently, after heparin injection, the electrophoretic peak of lipoproteins shifts toward the α-fraction. The studies showing this shift in ratio of β- to α-lipoproteins after heparin injection cannot be evaluated at present, since we do not know whether it is the breakdown of β-lipoproteins that causes the increase in the α-lipoproteins or a free molecular transfer amongst them.

Studies with radioactively labeled substances indicate that the fatty acids of chylomicrons are carried to the tissues (mainly adipose) and depending upon the nutritional status, and perhaps hormonal influences, they are either deposited or carried back to the plasma for energy requirements as unesterified fatty acids, with glucose being utilized preferentially. The whole scheme presented above of lipid metabolism involves many assumptions and displays wide gaps in our present knowledge. With this as the background, we can proceed on to examine the clinical investigations in the field.

Clinical Studies

Jones et al.,[34] 1955, studied the electrophoretic pattern of serum lipids in arteriosclerotic subjects and compared these with a group of hypothyroid patients. Although the total lipids were consistently elevated in both conditions, a significantly specific elevation was noted in the β-lipoprotein fraction in the arteriosclerotic group only. Bronte-Stewart, Keyes, and Brock,[35] 1955, studied 383 men of age groups between 40 to 58 years belonging to three different

racial groups—Bantu, Cape Colored, and Europeans. In this study the level of β-lipoproteins was shown to be parallel to the incidence of coronary artery disease.

Classifying the lipoproteins according to their densities and flotation rates in the ultracentrifuge as Svedburg units (S_f), Gofman [36] and many others have reported a specific correlation between human atherosclerosis and the (S_f) 12-20 class of lipoproteins. In sharp contrast, however, is the study of Paterson et al.,[22] where the only class of lipoproteins showing correlation with atherosclerosis was S_f 0-12. In the cooperative study on lipoproteins and atherosclerosis sponsored by the American Heart Association, in 1956, the committee members held divided opinions. Lewis et al.[25] concluded that people prone to develop atherosclerosis seem to have elevated S_f 20-100 lipoproteins and possibly S_f 12-20 particles; but these, or the calculated atherogenic index thereof, apparently have no more significance at present than serum cholesterol determination. The Gofman group, on the other hand, believed that lipoprotein measurements should be corrected for Ogston Johnston effect and felt that the resulting "standard" S_f lipoproteins of the 0-12 and 12-400 classes and their calculated atherogenic index (taking the latter class as 1.75 times more significant milligram for milligram) show a much closer relationship to atherogenesis when compared to serum cholesterol level alone. Chapman and associates,[37] 1956, tried autopsy correlation with the clinically determined atherogenic index and found no correlation at all.

Influence of Dietary Fats on Serum Lipids

Keyes and Anderson,[8] 1954, have brought forth statistical evidence that the incidence of atherosclerosis in various countries of the world roughly runs parallel to the percentage of calories obtained from fats in the diet. In the United States it is mentioned that about 40% of the total calories are derived from fats, while in countries like Japan and Africa, fat constitutes on average between 8% to 10% of the total caloric intake. The study of Bronte-Stewart and associates,[35] 1955, referred to earlier, is significant in the same respect, that the curve of fat consumption in three racial groups studied ran parallel to the level of serum lipids and incidence of coronary artery disease. Undoubtedly, in such large population studies, other important variables affecting the study are not accounted for. Some of these are the individual factors of perhaps psychic or hereditary nature, the different working requirements, and the difference in the types of food consumed. Attemps have been made to assess the influence of these factors. Keyes et al.[38] determined serum levels of cholesterol after a breakfast in persons accustomed to and without physical exercise. The sedentary group was noted to achieve a twofold rise in serum cholesterol. The authors suggested it to be one of the likely causes for susceptibility to atherosclerosis. The fact that in a country with high incidence of atherosclerosis like the United States people with all different kinds of working habits are afflicted with it would suggest that physical exercise is not a major factor. The role of heredity in this disease is also controversial. Page, Lewis, and Gilbert,[39] 1956, studied a group of Navajo Indians, supposedly a pure-blooded race, with dietary habits resembling an average American. The study revealed that the total serum cholesterol, the α- and β-lipoproteins, and the incidence of coronary artery disease in the Navajo Indians were significantly less as compared to American controls. Epstein et al.,[40] 1956, studied groups of Americans of Jewish and Italian extraction with a similar caloric and fat intake and similar working conditions. A higher rate of prevalence of hypercholesteremia and twice as much incidence of manifest coronary artery disease was found among the Jews as compared to the Italians. Recent studies by Keyes,[41] 1957, on people from same heritage

put under different environmental conditions present contrary evidence. These studies on Japanese men in Japan, Hawaii, and California revealed a parallelism between the amount of fats consumed in the diet, the level of serum cholesterol, and the incidence of atherosclerosis. In a separate study [42] Japanese coal miners were given a high-fat diet and were noted to respond to it by elevation of serum cholesterol in the same way as an American (Minnesota) would.

Clinical Trial of Low-Fat Diet

Morrison,[43] 1955, reported his observations on 100 patients with previous history of myocardial infarction, one-half of whom had their dietary fat restricted to 25 gm. daily and the other half of whom were given an unrestricted diet to serve as controls. A twofold mortality in the control group is recorded in a period extending to eight years. However, no conclusive evidence is yet available that dietary restriction of fats affects the course of the disease favorably in an atherosclerotic person. Indeed, Mann and Stare,[44] 1954, held that severe dietary restriction of fats below 50 gm. a day was unwise and against the principles of good nutrition.

The effect of such restriction of dietary fats on serum lipids has been variously reported. Hatch and associates,[45] 1955, studied a group of hypertensive patients for a period of several months with severe dietary fat restriction and found no decrease in the S_f 12-20 lipoproteins and actual increase in the S_f 20-100. Lyon et al.,[46] 1956, reported lowering of lipoprotein levels and atherogenic indices (Gofman) in 470 patients followed for a five-year period and taking a low-fat diet. Linquist and Isaksson [23] studied patients given a diet with severe dietary fat restriction and supplemented carbohydrates. They noted a decrease in total cholesterol mainly in the bound fraction. No change was recorded in the neutral fat.

Effects of the Type of Fat Consumed

The fact that humans in lower economic strata consumed cheaper priced fats and concomitantly showed a lower incidence of coronary atherosclerosis focused attention upon the effect of different types of fats on serum lipids. Kinsell et al.[47] 1952, and Ahrens and associates,[48] 1954, reported that serum cholesterol and phospholipids could be lowered by substituting fats of vegetable origin for animal fats in the diet. Groen et al.,[49] 1952, showed that an exclusively vegetable diet can lower the serum cholesterol even if fat content remains high. Bronte-Stewart and associates,[50] 1956, studied 10 patients with short-term experiments extending to two or three months, each patient being given a different type of diet for a few days. The effect of variation of vitamin and protein intake was taken into account. The animal fat and hydrogenated fats raised the serum cholesterol and phospholipids, while vegetable oils (olive and sunflower-seed oil) and marine oils lowered these lipids in the serum. Beveridge, Connell, and Mayer,[5] 1956, fed corn oil as 58% of the total caloric intake to a group of students and concluded that in spite of the additional fat consumption of animal origin the plasma cholesterol was lowered and the fall produced was greater than just simple fat restriction. Increase of the plasma cholesterol in controls given animal fats alone was demonstrated. Nicholes, Dobbins, and Gofman,[52] 1957, studied the effect of animal versus vegetable fat on serum lipids in five subjects, with each dietary experiment extending from 10 to 24 weeks. They concluded that the major cholesterol-bearing lipoproteins, i. e., standard S_f 0-12 and 12-20, were definitely higher when animal fat is consumed rather than the vegetable fat. The triglyceride-rich lipoproteins, i. e., standard S_f 20-100 and 100-400, were virtually independent of the type of fat consumed in diet, yet they went up when carbohydrates were substituted for fats isocalorically. On a reducing diet, both groups of lipoproteins were lowered. They further

concluded that lowering effect on the low-density lipoproteins was due to the absence of animal fat in diet and that no protective action of vegetable fats as such could be demonstrated. The authors point out the inadequacy of serum cholesterol measurements alone in such experiments because they may not show much change on account of the balancing effect of two classes of lipoproteins.

Statistical studies by Brozek et al.[53] 1957, in Yugoslavia on three groups of clinically healthy population revealed the serum cholesterol to be the highest in animal-fat, lowest in vegetable-fat, and intermediate in the low-fat consumption group.

In an attempt to find out the reason for such different behavior of dietary fats of animal and vegetable origin, Ahrans et al.[48] 1954, made the observation that highly unsaturated fats liquid at room temperature displayed on feeding the maximum efficacy to lower the serum lipids and that this effect could be reversed by hydrogenation of the same fats. Swell and associates,[54] 1955, confirmed the observation in animals that cholesterol, fed along with saturated fatty acids, gave rise to higher serum cholesterol levels as compared to when it was fed with unsaturated fatty acids. Other workers (Bronte-Stewart[50]) presented similar results. Sinclair,[55] 1956, has ventured a hypothesis as follows. Polyethenoid fatty acids are essential for the body and have to be supplied in the food as vitamins. The body can synthesize a fatty acid with one unsaturated bond only (oleic acid). Arachnodic acid containing four unsaturated bonds is the most important and can be synthesized in the body if dienoic acids (linoleic) are available. Pyridoxine (vitamin B_6), however, is necessary for this conversion. It is of interest to note that male requirements of essential fatty acids are five times greater than the female.

Evidence exists that cholesterol is normally esterified by unsaturated fatty acids.[20] In their absence, the cholesterol is obliged to combine with saturated fatty acids and may not be disposable by the tissues and thus may accumulate in the serum. In fact, rats given a fat-free diet have been shown to accumulate esterified cholesterol under their skin. Pyridoxine deficiency has been shown to cause atherosclerosis and sometimes hypertension in monkeys.[56]

Essential fatty acids are destroyed by hydrogenation, deep-frying, flour extraction, and deodorizing of oils. Unnatural fatty acids may be formed during these processes. The excess of saturated fat in diet, on the other hand, may act as an antivitamin and increase the requirements of essential fatty acids. Thus runs the postulate of Sinclair, suggesting that deficiency of essential fatty acids may be the basic cause of atherosclerosis.

Ancel Keyes,[57] 1956, presents the following objections to the above thesis: 1. In dietary experiments prolonged to four to six months with a low-fat diet, the supply of essential fatty acids would necessarily be very low, and still the blood cholesterol stays down. 2. Increased consumption of some fats, even along with increased supply of essential fatty acids, raises the serum cholesterol. As a result of their own experiments, Keyes and associates,[58] 1957, claim that serum cholesterol is more related to the total consumption of fat than to their degree of unsaturation or linoleic acid content. These conclusions are based on the facts that sunflower seed oil, which has maximum content of linoleic acid, and fish oils, poor in such fraction yet the most unsaturated of all oils, both produce on cross feeding experiments a statistically significant rise in the serum cholesterol after corn oil. The authors add that corn oil may have a special effect.

Ahrens et al.,[59] 1957, separated the nonsaponifiable fraction of corn oil by molecular distillation and, by feeding it in concentrated form, demonstrated that the serum-cholesterol-lowering ability of corn oil did not reside in this fraction. Further, to decide whether or not the degree of unsaturation or the linoleic acid content de-

termined the effect, the fatty acids were saponified and reesterified with glycerin in a random fashion. This caused no change in the serum-lipid-lowering effect. Further substitution of fatty acids with fatty acids of similar chain length was carried out, and the serum-lipid-lowering abilities of different fats were compared to their iodine value, linoleic acid content, and the biological activity on rats deficient in essential fatty acids. The closest relationship was achieved with the iodine values. These authors also demonstrated that the effect of corn oil was not due to its sterol content, and they failed to demonstrate any consistent rise after partial hydrogenation of corn oil. For sake of studying the effect of chain length of fatty acids, effects of cocoa and butter were studied. These two fats are similar in their iodine values and essential fatty acid content, yet butter, on account of short-chain acids, caused a greater rise in serum cholesterol. However, the objection stands that these formula types of diets are unphysiological, and it yet remains to be shown that addition of vegetable oils to a normal nonvegetarian diet can lower the serum cholesterol.

Vegetable Sterols

The serum-cholesterol-lowering activity of vegetable oils has been considered to be due to another fact also, and that is their vegetable sterol content.[51] Such compounds are supposed to delay the absorption of cholesterol from the intestine. The effect of β-sitosterol has been studied by various workers. Joyner and Kuo,[60] 1955, found that doses of 10 gm. daily of this agent produced reduction of serum cholesterol and β_1-lipoprotein fraction on unrestricted diets. Barber and Grant,[61] 1955, administering smaller dosages of β-sitosterol, reported only a slight reduction of serum cholesterol and a rise in the neutral fat and the total lipids. On larger dosage the same authors observed a more striking decrease of serum cholesterol. Farquhar et al.,[62] 1956, report a reduction of serum cholesterol and β-lipoproteins in 15 patients with previous myocardial infarctions on feeding β-sitosterol, irrespective of initial levels and contents of diet. Best and Duncan[63] report a uniform reduction in plasma and liver cholesterol on administration of sitosterol to hypothyroid and arteriosclerotic[64] patients and to experimental animals given a free diet. No toxic effects of any kind were noted from sitosterol. The dosage used was 20-25 gm. daily. It has been suggested that β-sitosterol might act by competing with and inhibiting intestinal absorption of exogenous cholesterol. Friedman et al.,[65] 1956, could demonstrate only a slight retarding effect of β-sitosterol administration on cholesterol absorption in rats. Successful inhibition has been reported earlier in chickens and rabbits by Patterson,[66] 1951.

The above discussion, in the present state of our knowledge, does not permit any teleological conclusions. J. C. Peters concludes that restriction of fat in the diet may reduce the serum lipids of some of those who demonstrate pathological lactescence, in other words, in whom neutral fat is increased in the serum. In nonlactescent serum, a low-fat diet seems to be without much effect. It may be possible to reduce some of these by changing to vegetable oils or by administration of vegetable sterols. Whether such lowering would ultimately affect the prognosis of coronary artery disease or not remains undetermined. Yet, most of the physicians today restrict fats in the diet of their patients suffering from coronary artery disease.

Heparin

Heparin is physiologically produced by mast cells of the reticuloendothelial system, is suspected as serving as one among the intravascular anticoagulation mechanisms, and may have other hitherto unknown functions.

Much has been elucidated since the original observation of Hahn,[67] 1943, that the intravenous injection of heparin clears the alimentary lipemia present in dogs. Ander-

son and Fawcett,[68] 1956, observed that heparin changes an opalescent plasma of a human drawn after a meal to a clear plasma. Kory et al.,[69] however, failed to observe any change in the heparin in fasting or post-fatty-meal serum turbidity measured calorimetrically.

Grahm et al.,[70] 1951, observed that a single injection of heparin immediately caused changes in the lipoprotein pattern. The effect reached a maximum in 3 hours and reverted to its original level in a period of 24 hours. This effect is seen only in vivo and consists of the conversion of low-density lipoproteins with faster flotation rates in the ultracentrifuge to lipoproteins with higher density and slower flotation rates. Rinzler et al.,[71] 1953, could detect no change in lipoprotein pattern after eight weeks of twice-weekly administration of heparin in nine patients. Anfinsen,[32] 1954, as referred to earlier, believes that studies showing such transient shift in β- to α-lipoprotein ratio are of little significance.

Release of free fatty acids in the blood and the lymph has been noted after heparin administration.[72] The effect is due to the breaking up of bonds in the triglycerides and is seen only in vivo. This suggests the nature of action of heparin to be enzymatic in character[73] (lipoprotein lipase). The enzyme responsible is in all probability an esterase that has been purified and characterized but not yet chemically identified.[74] Heparin most likely forms prosthetic group of this enzyme because protamine can block its action.[32] Day and co-workers,[75] 1957, demonstrated a sharp rise in total esterified fatty acid level in alimentary lipemic serum of young persons after intravenous protamine, and this was not observed in older age groups with or without clinical atherosclerosis. No significant change was noted in cholesterol content, visible lipemia, or phospholipids in any of the groups. The authors concluded that while in young persons heparin had a physiological action in fat transport, with advancing age there occurred a deficiency in circulating amount of heparin, and this accounted for a poor fat tolerance seen in the aged. Barker,[76] 1957, stresses the importance of investigating the "heparin-activated clearing factor" under uniform and standardized conditions. On so performing the tests on 121 subjects and analyzing them statistically, he could not find any evidence of retardation of this activity with advancing age or in atherosclerotic persons. He further suggests that the reduced fat tolerance in the aged is probably of gastrointestinal origin, as Herbst et al.,[77] 1956, have shown that intravenous administration of fat emulsions evokes a response of decrease in serum lipids and a change in electrophoretic patterns similar to heparin in normal humans during alimentary lipemia and in patients with idiopathic hyperlipemia. Future work along these lines is awaited with interest because of some therapeutic pathways which it might open toward management of atherosclerosis. In animal experiments the development of atherosclerosis in cholesterol-fed rabbits has been shown to be retarded under the influence of heparin.[78] Some cases of essential hyperlipemia in humans have been reported to respond to heparin.[79]

Some fascinating postulates are presented in the literature[80] about other possible effects of heparin, closely related to its action on blood lipids. Heparin has been demonstrated to abolish the increased coagulability, viscosity, and adhesiveness of blood elements, all of which can be shown to be caused by high lipid content of the serum, while no such effects occur with anticoagulants of the coumarin series. Heparin has been further demonstrated[81] to increase the A-V oxygen difference taken from the forearms of atherosclerotic persons. It is postulated that heparin increases the O_2 uptake of the tissues by removing a film around the tissues which is formed by lipids and thus hinders oxygenation. These postulates infer two additional actions of heparin on blood other than its anticoagulant effect, the first of these being an antithrombus action by limiting adhesiveness of blood elements and the second one, improving the flow of

blood by diminishing its viscosity. Engelberg [82] recorded changes in ballistocardiogram after an injection of heparin and thought that they could be attributed to the action of heparin on the viscosity and flow of the blood. The action on O_2 uptake of the tissues has been presumed to effect a better oxygenation of the myocardium and is presented as an explanation of subjective improvement in patients with angina pectoris.

Contradicting reports are available about the therapeutic effects of heparin in angina pectoris. Grahm et al.,[70] 1951, reported reduction in angina in 55 out of 59 patients receiving heparin for one to eight months. Engelberg,[82] 1952, followed 29 patients given heparin twice weekly for a period of 6 to 12 months and reported subjective improvement in 55% of them. Immediate ballistocardiographic changes were interpreted as improvement. More significant improvement was noted in the two-step Master's exercise tolerance in the electrocardiograms. Russek,[83] 1952, failed to detect any change in 14 patients on performing an exercise-tolerance test before and 24 hours after an injection of heparin. Binder et al.,[84] 1953, administered alternate heparin and saline injections to 34 patients twice a week for two months and could not detect any beneficial effect. Grunner et al.,[85] 1953, administered placebo injections twice a week for 2 to 4 weeks followed by 7 to 11 weeks of heparin in 27 patients. No subjective improvement or electrocardiographic changes were noted. Rinzler,[71] 1953, studied 18 patients with placebo controls and twice-a-week heparin for eight weeks and reported no effect on electrocardiogram, ballistocardiogram, or subjective pain.

It is obvious that all studies reporting negative results with heparin have been limited to a comparatively short length of time. In the longest study, extending to 12 months, improvement was reported in 55% of patients. The vagary of assessing the response on electrocardiographic and ballistocardiographic criteria is obvious. Hence, it remains yet to be refuted that long-term therapy with heparin could have a retarding influence on atherosclerosis.

Unless the cost is too great a consideration, it is recommended that long-term therapy with heparin be tried in patients with coronary artery disease. The dosage used in the past has been 100 to 200 mg. subcutaneously twice a week. This dosage has little or no significant effect on the coagulation mechanism. There are no other toxic effects from such an administration of heparin. The patient can be taught to inject it himself.

Lipotropic Factors and Vitamins in Atherosclerosis

The ability of choline to prevent fatty changes in the liver of a depancreatized animal earned it the recognition of a lipotropic factor. Choline [86] is the cation which, when attached to phosphoric acid, enters into formation of lecithins, the most important phospholipid concerned in transport of neutral fats in the body fluids. This is achieved by virtue of their being soluble in water and emulsifying and solubilizing the fats and cholesterol.

Choline, 2-hydroxyethyl-trimethylammonium, can be easily synthesized in the animal body in its entire structure, except the methyl groups, which have to come from external sources. Methionine is the principal methyl donor in the body; betaine has similar functions. Inisotol as a component of a cephalin probably acts like lecithin in fat transport under certain circumstances. It acts as a lipotropic agent only when added to hypolipotropic diet devoid of fat. On the basis of the above evidence, choline has been tried and reported to resolve aortic atherosclerosis in experimental animals.[87] Morrison and Gonzalez,[88] 1950, reported in an observation on 115 survivors of myocardial infarction against an equal number of controls that feeding 12 gm. of choline daily for a period of one to three years reduced the subsequent mortality in this group. According to Labeck,[89] 1955, choline administration increases the phospholipids

and decreases the chylomicrons. Other workers have failed to confirm these findings. Sherber and Levites,[90] 1953, could not produce any fall in serum levels of cholesterol in patients by use of choline and inisotol alone. Ridout et al.,[91] 1954, on the other hand, observed that abolishing choline from the diet of rats produced a fall in serum cholesterol below normal values. This fall can be corrected by choline, betaine, and cyanocobalamin (vitamin B_{12}) but not by inisotol.[92] Low concentrations of phospholipids perhaps keep the cholesterol down. In fact, feeding cholesterol to choline-deficient rats does aggravate the cardiovascular lesions.[93]

Synthetic agents capable of lowering the surface tension and having an emulsifying action on fats similar to lecithin have been employed for this purpose. Sherber and Levites,[90] 1953, used polysorbate 80 (Tween 80) along with choline and inisotol on 16 patients and reported that while they with the combination of all three agents. did not get any effect with these components individually, they did obtain a lowering of serum cholesterol of a significant degree The serum cholesterol returned to original levels as soon as the drugs were stopped. They further demonstrated that this decrease in cholesterol was accompanied by an increase in steroid output from the adrenal and also increased excretion of cholesterol in the urine. It is interesting to point out here that corticotropin (ACTH) administration causes a rapid fall of cholesterol content of the adrenal gland, while cortisone has no such effect. Laurendeau and Denis,[94] 1954, showed a decrease in the total and the esterified cholesterol, an increase in the phospholipid, and a reversal of a postive cephalin-flocculation test in more than half of the 13 patients treated with polysorbate 80 and a mixture of lipotropic substances for five months. They also indicated that out of 131 arteriosclerotic patients selected to exclude any obvious concomitant liver disease a significant number showed a hyperglobinemia and positive flocculation tests, some of which reverted to normal after above therapy. This tends to suggest, though rather mutely, the possible existence of an underlying deficiency state. Di Luzio,[95] 1955, however, failed to demonstrate any choline deficiency in cholesterol-fed rabbits. Pyridoxine deficiency, however, has been suggested by Schroeder,[56] 1955, as a possible cause of atherosclerosis. The diet, unless fresh, he believes, is deficient in this vitamin, and such deficiency may be further conditioned by the presence of trace elements in the diet. The role of pyridoxine in synthesis of polyethenoid fatty acids has already been mentioned (Sinclair [55]).

All the fat-soluble vitamins except vitamin K have been implicated to have a role in atherosclerosis. Weitzel,[96] 1957, demonstrated in atherosclerotic chickens that large doses of vitamin A caused a striking diminution of fatty plaques in the arteries microscopically and produced a considerable drop in the total fat, neutral fat, phospholipids, and cholesterol content of the aorta. Addition of vitamin E potentiated this action, although by itself its action on plaques was much weaker and the drop in aortic lipids mainly comprised neutral fat.

Gervasoni and Vannotti [96] made a clinical trial on patients by administering 300 mg. of vitamin E and 22,000 units of vitamin A orally. The total serum cholesterol and phospholipids were noted to actually increase. The authors explain it on account of increased mobilization of lipids by inhibition of fat deposits. De Langen and Donath,[97] 1956, fed large doses of vitamin D to animals and produced lesions in the aorta and small arteries. Simultaneously fed cholesterol was more effective in producing atheromatous lesions. The authors point out the hazard of feeding extra vitamin D to older people. The injurious effect may come on years later.

No recommendations can be made for therapy today with regard to lipotropic agents, vitamins, and their relationship to atherosclerosis.

Hormones and Atherosclerosis

Estrogens.—The striking immunity of premenopausal women to coronary artery disease led to the idea that estrogens must have a protective influence on this disease. After the menopause the cholesterol in the serum goes up, and this has been explained on account of the lack of ovarian hormone synthesis. Oophorectomy in a young female tends to make her more susceptible to coronary artery disease, while elderly men with prostatic cancer treated with estrogens were noted to gain improvement regarding their coronary artery disease.

Experimentally, according to Katz,[98] 1953, estrogens inhibit coronary atherosclerosis when given to cholesterol-fed cockerels without exerting much effect on aortic atherosclerosis. In the same animals, increase in phospholipid and in the ratio of α- to β-lipoprotein was demonstrated. Androgens administered to these animals counteracted the feminizing effects of estrogens without interfering with the effects on cholesterol-induced atherogenesis. On the other hand, the female rabbit is known to be more susceptible to experimental atherosclerosis, and testosterone prevents the effects of cholesterol feeding in this animal.

Clinical trials are broadly in accord with each other. Oliver and Boyd,[99] 1956, administered estrogens to 100 survivors of myocardial infarction and noted a reversal to normal in total cholesterol and the cholesterol-phospholipid ratio. The phospholipids increased, and the cholesterol contained as β-lipoprotein was lowered. Loss of libido and gynecomastia were reported to be well tolerated by patients and were not ameliorated by androgen therapy, which, however, anulled the beneficial effects on serum lipids. Russ and Barr,[100] 1955, reported similar results.

Robinson et al.,[101] 1956, treated 51 survivors of a myocardial infarction for a period of one year. In addition to similar results on cholesterol and lipoproteins, thyroid function as measured by iodine uptake was shown not to be altered. Testicular biopsies were done to show progressive fibrosis and destruction of cells, which was almost complete within a period of one year. Engelberg and Glass,[102] 1955, administered physiologic doses of different steroid hormones and failed to demonstrate any consistent change in serum lipids or lipoprotein patterns.

Hence the therapy with effective doses of female hormones carries the risk of permanent and complete castration in the males. Their trial has to be evaluated considering the same. While the loss of libido and impotence may not be acceptable to a younger person, the older people frequently may develop a mental depression. Most workers do not recommend the use of estrogens in treating arteriosclerosis in males at this time. On the other hand, their use in the female patients affected with coronary artery disease is justified, and it is recommended that a surgically induced menopause in a young woman should be treated with these agents.

Thyroid and Treatment of Coronary Artery Disease

Katz and associates,[103] 1954, demonstrated the tendency of thyroid hormones to antagonize the hypercholesteremia and atherogenic effect that can be produced experimentally in rabbits and chickens by feeding cholesterol. However, such effects of these hormones were found to be rather inconsistent. In other animals, such as dogs and rats, hypercholesteremia cannot be produced unless the thyroid is ablated.[20] Strisower et al.,[104] 1954, studied the effect of thyroid extract on serum lipoproteins and cholesterol in humans. A fall in the level of serum cholesterol and S_f 0-12 and 12-20 lipoproteins was achieved, with no effect demonstrable on S_f 20-400 group. This was accompanied by negative caloric balance, and the authors wondered if that could not be the entire basis for the above effects. Jones and co-workers,[84] 1955, compared lipoprotein patterns in hypothyroidism, hyperthyroidism, and coronary atheroscle-

rosis. The study revealed that although for a given degree of hypercholesteremia the atherosclerotic group showed greater β-lipoproteinemia, yet no dividing lines could be drawn through the spectrum of lipoproteins separating thyroid hypofunction and atherogenesis. Other features differentiating the hyperlipemia of hypothyroidism and that of atherosclerosis are preservation of the normal interrelation between cholesterol and phospholipids and lack of any significant elevation of neutral fat. The lipid accumulation in hypofunction of thyroid is on the basis of over-all retardation of synthesis, destruction, and excretion of cholesterol.[20]

Two opposing lines of therapy have been recommended for coronary artery disease, so far as function of thyroid gland is concerned. Blumgart and associates,[105] 1953, have recommended induction of hypothyroidism for the patient incapacitated because of angina. In fact, they feel that unless a contraindication exists, antithyroid treatment should be tried on all patients before subjecting them to more drastic surgical procedures, which should be reserved for the failures of such treatment. The objection that hypercholesteremia resulting from induced hypothyroidism in patients might aggravate the process of atherosclerosis is not valid in the opinion of above authors. No convincing data are available indicating the incidence of atherosclerosis in hypothyroid persons. The aforementioned investigators[101] followed patients after total thyroidectomies who had elevated cholesterol values and no known stigmata of atherosclerosis. Some of these patients came to autopsy within a period of 1 to 13 years after removal of the thyroid gland and are reported to have shown a minimal evidence only for coronary atherosclerosis.

The method advocated by Blumgart and Freedberg,[107] 1952, is to induce hypothyroidism by divided doses of radioactive iodine. A single large dose may bring on an initial peak of hypermetabolism and make the patient worse and prove dangerous. The antithyroid drugs, like thiouracil, are much inferior to radioactive iodine for this purpose.[108] It is much more difficult to control the thyroid status of the patient while he is being given these drugs, and he runs the additional risk of drug reactions, especially agranulocytosis. These drugs, however, can be employed to predict the response to treatment before instituting the permanent measure with radioactive iodine. After the induction of the hypothyroid state, the patient is given such small doses of thyroid extract orally as are compatible with his comfort and also as will avoid the undesirable effects of hypothyroidism as far as possible.

Three patients out of four receiving antithyroid treatment for incapacitating angina are reported to improve, according to Blumgart. Comparable results are reported by others.[108]

Contraindications to this treatment as mentioned by Blumgart,[105] 1953, are rapidly progressive disease, such as malignant hypertension, spyhilitic aortitis, existing hypothyroidism, active rheumatic fever, recent myocardial infarction, bronchiectasis, cirrhosis of the liver, and emotional instability. The treatment may take six months to become effective.

The second line of treatment employs the serum-cholesterol-lowering ability of thyroid hormones at a risk of accelerating the rate of metabolism. Various analogues of thyroid hormones have been tested for greater suitability. Oliver and Boyd,[109] 1957, tried triidothyroacetic acid in euthyroid persons suffering from coronary artery disease. A temporary fall in total cholesterol, the cholesterol fraction in β-lipoproteins, and cholesterol-phosphorus ratio was reported. This effect disappeared after a few weeks; further increase in dosage produced little effect, and discontinuance gave rise to a small rebound above the original level. Although there was no significant concomitant rise in B. M. R. with this preparation, yet it made the angina worse in two of the patients. There was a suggestive evidence

that it raised the oxygen requirements of the myocardium without causing an apparent rise in B. M. R. The authors concluded that it is unlikely that any such agent would be suitable for treatment of hypercholesteremia of coronary artery disease.

Strisower and co-workers,[110] 1957, employing dried thyroid extract to study its long-term effects on serum lipoproteins and cholesterol levels, concluded that the "escape phenomenon" or tolerance is explained by depression of endogenous thyroid hormone, and the effect could be maintained by increase in dosage. The response involved, the lowering of S_f 0-12 and 12-20 lipoproteins (standard S_f), and the calculated atherogenic indices were then improved.

The authors suggest that thyroid extract is worthy of consideration as prophylaxis against coronary artery disease, although more should be known about the interrelation of thyroid function and lipoprotein metabolism before it can be recommended for clinical trial.

Coronary Vasodilators

Wegria,[111] 1951, presents an extensive review of the actions of drugs on the coronary circulation. He points out that to evaluate the action of a drug on coronary vessels and accept it as a beneficial agent one must know the action of the drug not only on coronary flow but also on the cardiac work and efficiency as well as on the extravascular support provided by the myocardium. This entails the simultaneous study of the action of the drug on the blood pressure, the size of the cardiac chambers, the strength of the myocardial contraction, the cardiac output, the O_2 consumption by the heart muscle, the flow of blood in coronary arteries, and the changes in the resistance offered to such flow. To our knowledge, such extensive studies are not available on any single therapeutic agent. Silber and Katz,[112] 1953, stressed the fallacy of employing subjective relief of pain and electrocardiographic improvement in exercise tolerance as an indication of changes in the coronary blood flow. These factors account for the presence of contradicting reports in literature about the efficacy of various drugs in treatment of coronary insufficiency.

Foltz et al.,[113] 1950, measuring the coronary blood flow by flotameter method and calculating the myocardial oxygen consumption from arteriovenous difference, indicate that nitrites increase the coronary blood flow without increasing the oxygen consumption of the myocardium, while aminophylline increases the oxygen consumption and hence the cardiac work concomitant with increase in coronary blood flow. Eckstein,[114] 1951, presents similar evidence that acetylcholine and glyceryl trinitrate (nitroglycerin) increase the efficiency of the myocardium. Wolf and Berne,[115] 1956, have shown aminophylline, nikethamides, and nucleotides to have an opposite effect of decreasing the myocardial efficiency by causing an increase in cardiac work along with increase in coronary blood flow. Evidence of a possible antiadrenergic effect of glyceryl trinitrate has been presented but not substantiated.[116] In animal experiments administration of sodium nitrite promoted interarterial coronary anastomosis both in normal hearts and after coronary occlusion.[117] On the basis of the above evidence, aminophylline may not be recommended for long-term and prophylactic use.

Clinical and experimental evidence in favor of nitrites has been presented by several authors. Russek et al.,[118] 1955, report that oral pentaerythritol and sublingual glyceryl trinitrate prevented the electrocardiographic effects of coronary insufficiency in patients, while several other drugs failed to do so.

Kalmanson [119] and Kory,[69] 1955, failed to confirm these findings. Weitzman,[120] 1953, using much larger doses (60 mg. t. i. d.) on long-term basis, reported clinical improvement in 14 out of 30 patients. Winsor and Humphreys,[121] 1952, noted that the relief was greater in severer cases of angina treated with this agent.

Riseman et al.,[122] compared the immediate effect of the administration of cinchona alkaloids on the anginal pain and the electrocardiogram to administration of glyceryl trinitrate and pentaerythritol (Peritrate). These authors concluded that the effect of cinchona alkaloids were better than those of pentaerythritol and were less as compared to glyceryl trinitrate. Patients who failed to show a response to glyceryl trinitrate did not respond to these alkaloids either.

The weight of evidence in case of other drugs, such as Visammin (2-methyl-5,8-dimethoxyfuranochrome), papaverine, and aminotrate phosphate (Metamine) swings to the direction that they are not nearly as useful as nitrites.[123]

Anticoagulants

Although anticoagulant drugs have an established place today in therapy of an acute attack of myocardial infarction and fair agreement exists that acute coronary insufficiency or impending myocardial infarction should be treated exactly like an acute attack, the long-term prophylactic anticoagulant therapy in hope of preventing the subsequent episode still awaits the verdict of conclusive evaluation. Wright et al.[124,125] have provided evidence by analyzing the follow-up of patients with various cardiovascular disorders given long-term anticoagulants that subsequent episodes of thromboembolism were reduced. Keyes et al.[126,127] have followed patients with previous myocardial infarction, classifying them into single- and multiple-attack groups, with long-term anticoagulant therapy, and a control group in the same time period and concluded that the mortality was significantly less in the treated group during a period of five years.

Suzman et al.,[128] 1955, followed patients with controls whom they analyzed according to both previous history of coronary artery disease and the severity of presenting attack of myocardial infarction. These authors concluded that severe cases treated with long-term anticoagulants showed statistically significant decrease in mortality and incidence of subsequent myocardial infarction. Incidence of angina and myocardial failure were not affected. They further concluded that mild cases had a much better outlook and did not behave any differently whether they were treated or not. The authors recognize the fact that treated patients in their group received a much closer medical supervision and displayed a sense of security. How much these factors could influence the results remains to be determined. A double-blind placebo-controlled study has not been done. Further, at present we do not know when it should be safe to discontinue such long-term anticoagulant therapy after it has been once started, not speaking about any risks that it may carry with it.

Surgical Approach

The comment here shall be confined to only those surgical procedures that have been designed to improve the blood supply and oxygenation of myocardium. Three main types of approaches have been made to achieve better supply of blood to the myocardium. These are attempts (*a*) to promote intercoronary anastomosis, (*b*) to bring extracardiac blood channels to the myocardium, and (*c*) to use the venous end of coronary circulation for perfusion of arterial blood or to increase the pressure of backward flow.

Thompson and Plachta,[129] 1954, recommend insertion of a nonabsorbable irritating substance, magnesium trisilicate (talc) inside the pericardial sac. This produces an acute inflammatory reaction followed by chronic granulomatous pericarditis, and the authors believe that this remains active for the rest of the life of the patient. Evidence of this activity has been demonstrated after 10 years in postmortem examination on some cases.

Clinical and electrocardiographic improvement in patients and reduction of mortality to 50% in animals after ligation of anterior descending branch of left coronary artery

is presented in support of the functional value of the procedure. In addition to angina pectoris, the operation is also recommended in hypertensive and valvular heart disease where myocardial failure may be the main disabling cause. Good results have been claimed in hypertensive cardiovascular disease even with enlarged hearts where the procedure is expected to prevent or improve the coronary insufficiency. The simplicity of the procedure has been mentioned as the front shield for its justification.

Burchell,[130] 1940, injected lead acetate agar (Schlesinger's mass) into the blood vessels in pericardial adhesions after experimental coronary ligation and observed that this material did not enter the coronary circulation. Since this material has been shown not to be able to enter vessels smaller than 40μ, it was concluded that the intact pericardium constitutes a barrier to vessels of a size greater than this.

Harken and associates,[131] 1955, observe that in all the diversified attempts at myocardial revascularization surprisingly similar clinical and experimental results are reported. These authors conclude that the mechanism of improvement underlying all these may be nonspecific to all of them. Suggesting further that breach of the epicardium may be responsible for the formation of better collaterals, these authors recommend application of 95% phenol as the only safe and effective agent for deepicardialization.

Beck and associates,[132] 1955, include mechanical abrasion of the epicardium and parietal pericardium in their procedure for helping coronary artery disease. These investigators used powdered asbestos as the irritating substance to instill in the pericardial sac and carry on a partial ligation of the coronary sinus. The authors[133] maintain that the mechanism of immediate death following occlusion of a branch of the coronary arterial system in great majority of the patients is development of ventricular fibrillation, triggered by the irritative action of the ischemic myocardium. It is further[134] suggested that very small increase in the amount of oxygen supplied to the myocardium may make the difference in preserving the normal cardiac mechanism.

The above authors[132] believe that the partial ligation of coronary sinus imparts such protection from immediate "mechanism death" by causing venous congestion.

It has long been known that there are venous channels in the myocardium opening directly into the cavity of the heart. Anastomosis can be demonstrated in normal myocardium between tributaries of coronary-myocardial sinusoids, Thebesian vessels, and cavity of right atrium. Forty per cent of the venous blood is drained by deep or thebesian system and sixty per cent by the superficial (anterior cardiac veins and coronary sinus system).[135] This anatomical fact encouraged the ventures that the deep system of veins may be made to take the whole job of venous return of the heart and the coronary sinus may be partially ligated or perfused with arterial blood through a graft. Arterialization of coronary sinus has been practiced and almost abandoned by the same investigators and others. It was postulated that such procedure would send arterial blood to the myocardial capillaries. These claims have not been substantiated by experimental studies.[136] There is unanimity of opinion about arterialization of coronary sinus that the graft remains functioning only for five to eight weeks.[137] After such period of time the veins become thick-walled and the blood can be shown to traverse the intercoronary anastomosis and bypass the capillary bed and so remain arterial in type. Gregg,[138] 1956, has presented experimental observations that even before five weeks the evidence for this blood traversing through the capillary bed of the myocardium is obtained only when the peripheral end of an artery is allowed to bleed, in which case the blood so obtained is unsaturated in oxygen content. The author further maintains that out of the experimental method on animals designed to

improve coronary flow, chronic ligation of a coronary artery itself gives rise to maximum figures of measured retrograde flow.

Considering that coronary circulation has already undergone an effect comparable to chronic ligation in a patient with arteriosclerotic heart disease, the additional measure of protection against fibrillation afforded by procedures like partial ligation of coronary sinus or extracardiac supply of collateral must be very small. However, it remains to be an unsettled question today.

Another ingenious attempt to increase the myocardial blood supply from extracardiac source has been made by Vineberg,[139] 1955. Quoting Schlesinger, he maintains that arteriosclerotic disease of coronary vessels affects predominantly the subepicardial course of the vessels, the deeper vessels remaining comparatively free. The author further observes that the anatomical peculiarity of myocardial blood supply includes the wandering course of anastomosing sinusoids, hence the free cut end of an implanted exocardiac vessel can be left embedded inside the layers of myocardial muscle without getting its lumen obliterated or formation of a hematoma. The author claims that the best results are obtained in cases where artery is implanted in an ischemic low-pressure area in preference to normal myocardium and in those in whom the procedure is done in experienced hands. No proof is available that the blood so supplied to the myocardium traverses its capillaries. In favor of the fact that this happens, the author has used an indirect argument by measuring the oxygen content of the coronary sinus blood after implantation of internal mammary artery and observing that these values were appreciably lower as compared to the arterial blood oxygen content. Neptune,[140] however, failed to inject the myocardial capillary bed through the anastomosis, using 40% gelatin solution containing colloidal suspension of carbon particles. Recently claims have been made that simple ligation of internal mammary artery not only results in relief of angina but also is a means of increasing blood supply to the myocardium.[141]

The exact worth of all these procedures is still debatable.[142] It is difficult to quantitate improvement in any given case. It is not valid to predict the course of the disease and not convincing to presume what might have occurred if the procedure was not done. On the other hand, postoperative results presented by various investigators leave little doubt that these procedures in some of the cases do affect clinical improvement even though it be temporary and nonspecific. In fact, at the moment we are not sure if the fact has been decisively disproved that the interruption of neuronal pain pathways during such procedures is not responsible for relief of anginal pain, especially for the overzealous reports of its disappearance immediately postoperatively. It is noteworthy in this regard that the thoracic cardiac nerves, rather than the cervical sympathetic, contain the major share of cardiac pain fibers.[143]

Experimental methods in animals performed in support of these procedures present a discrepancy greater than usual of translation in human terms. Further, most of the deductions made in these experiments are indirect, and it remains to be shown that increase in blood supply affected by any of these procedures actually increases the flow in the capillaries of the myocardium.

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Evolution of Modern Medicine

T. J. Maclagan and the Treatment of Rheumatic Fever with Salicin

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By some strange quirk of fate, the medical profession has almost forgotten the work and influence of a man whose contemporaries placed him beside Lister, the father of antiseptic surgery, and Simpson, the first physician to use chloroform in childbirth. Thomas John Maclagan, M.D. (Edinburgh), M.R.C.P. (London), discovered the action of the salicylates in rheumatism. The medical profession eulogized him with these words:

> The death of Dr. Thomas John Maclagan . . . has removed from our midst a medical man who has conferred an unspeakable boon upon suffering mankind. The great work for which his name is, or should be, ever memorable is the discovery of the curative action of salicin and arising from that of the salicylates upon rheumatism. That method at once revolutionized the treatment of a most formidable malady, which was brought under the control of the physician in a striking manner, not only as regards severity of symptoms and the duration of attack, but also in prevention of sequelae. There is no more definite thing in the whole range of practical medicine than the specific influence of drugs of the salicyl group upon acute rheumatism. Indeed, the action of salicin and the salicylates in that complaint entitles them to be added to the scanty list of specific remedies in the possession of scientific medicine. It is difficult always to look at contemporary events in their proper perspective, but it seems certain that Thomas Maclagan deserves a niche in the temple of Fame as one of the great benefactors of the human race.[1]

Our interest in Thomas Maclagan was stirred originally by references to "the kindly, omniscient Scot" and the "wonder-working Maclagan"[2] in William J. Maloney's foreword to Leopold Lichtwitz's monograph, "Pathology and Therapy of Rheumatic Fever." It was the belief of Maloney's wise old Latin teacher that God has created a remedy for every illness and that these remedies are waiting for those who seek them. In support of his theory, the dominie told how Thomas Maclagan, who had been his boyhood friend in Perth, had found the cure for rheumatism by looking for the remedy where the disease was most prevalent.

"The employment of salicin in the treatment of acute rheumatism was no haphazard experiment, but had a fair foundation in reason and analogy."[3] So wrote Maclagan in March, 1876, two years after the idea of using salicin had first occurred to him.

> Rheumatic fever is now-a-days generally regarded as being produced by some cause or agency which is generated within the body. My own investigations into its pathology have led me to reject this view, and to adopt the old "miasmatic" view of its mode of origin, according to which the cause which gives rise to the disease is introduced into the system from without.
>
> Holding this view as to the pathology of rheumatic fever, impressed with the points of resemblance between it and intermittent fever, and bearing in mind that we have in quinine a potent remedy against the latter, there seemed to me good reason for indulging the hope that some remedy would yet be discovered capable of exercising a similar, if not equally beneficial action on rheumatic fever.
>
> . . . nature seeming to produce the remedy under climatic conditions similar to those which give rise to the disease . . . it seemed to me that a remedy for that disease would most hopefully be looked for among those plants and trees whose favourite habitat presented conditions analogous to those under which the rheumatic miasma seemed

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most to prevail. A low-lying, damp locality, with a cold, rather than warm, climate, gives the conditions under which rheumatic fever is most readily produced. On reflection, it seemed to me that plants whose haunts best corresponded to such a description were those belonging to the natural order Salicaceae, the various forms of willow. Among the Salicaceae, therefore, I determined to search for a remedy for acute rheumatism. The bark of many species of willow contains a bitter principle called salicin. This principle was exactly what I wanted: to it, therefore, I determined to have recourse.[2]

That the idea had, relatively speaking, a "fair foundation in reason and analogy" can be appreciated if the state of medical knowledge and opinion at that time is recalled. Rheumatic fever had been recognized as a disease entity since 1797,[4] but a specific remedy was lacking. In 1874, Lister had just begun to treat wounds with strong carbolic acid. Louis Pasteur's germ theory was being vigorously debated. The clinical thermometer had recently been developed to the point where practitioners were beginning to use it.[5]

When, in November, 1874, the idea first occurred to Maclagan to treat acute rheumatism with salicin, he himself took 5, then 10, and finally 30 grains and felt no discomfort or inconvenience. Thus assured of its safety, he gave 12 grains every three hours to a patient with well-marked symptoms of rheumatism. The results far exceeded Maclagan's most favorable expectations. Within two days the patient's temperature was normal and the pain was all but gone, though the joints remained stiff. The patient convalesced steadily and rapidly.[3] Details of eight cases of rheumatism successfully treated with salicin were reported by Maclagan in 1876.[3]

These remarkable findings were published at a time when the treatment of acute rheumatism was most unsatisfactory. Some physicians reported that a purely expectant plan of treatment—giving no drugs at all—seemed as effective as any of the usual remedies—purgatives, diaphoretics, sedatives, alkalies and alkaline salts, colchicum, aconite, quinine, Guajacum, lemon juice, sulfur, mercury, veratrine, tincture of muriate of iron, whey, and bread pills.

The tonic and antipyretic properties of salicin had long been recognized, and it had been used unsuccessfully as a substitute for quinine. At the time that Maclagan suggested its use in rheumatic fever, however, salicin had fallen into disuse and had even been dropped from the British Pharmacopoeia.

On the basis of his clinical observations, Maclagan drew the following conclusions: Salicin is a valuable remedy for acute rheumatism—the more acute the case, the more marked the benefit. The beneficial action in acute cases is generally apparent in 24 hours and always within 48 hours, provided the dose is large enough. Given at the beginning of an attack, it seems to arrest the course of the illness as effectively as quinine cures an ague, or ipecac, a dysentery. Salicin produces early relief from pain. In acute cases, the pain is sometimes relieved before temperature falls. This phenomenon is observed most often in patients with a nervous temperament whose pain is out of proportion to the fever. In chronic rheumatism, salicin sometimes does good where other remedies fail, but it also fails in some cases where other remedies succeed.

Although Maclagan was not certain of the effect of salicin on the cardiac complications of rheumatic fever, he believed that a remedy which shortened the duration or lessened the severity of an attack must reduce in a proportionate degree the "risk of cardiac mischief."[3]

The suggested dosage of salicin was 10 to 20 grains every two, three, or four hours in severe cases and 15 grains every three hours as a medium dose for an acute case. Maclagan did not bother to find the minimum therapeutic dose, because he was certain that a massive dose could be given without any discomfort or unpleasant side-effects.

In view of the subsequent bitter controversy regarding the relative merits of salicin and salicylic acid, it is of interest that

Maclagan in this original article described his experience with one patient treated with salicylic acid: "It seemed to do good to the rheumatism; but it caused so much irritation of the throat and stomach that I did not repeat it."[3] Maclagan concluded:

I shall be greatly obliged if those who try the remedy, and do not care to publish their observations, would kindly forward to me the results of their experience, be it favourable or otherwise. The points to be specially noted are the state of the patient, before taking the salicin, as regards heart, pulse, temperature, skin, tongue, urine, joints, &c., with daily (or more frequent) observations of the same points under its influence. Observation taken only once a day, to be taken as nearly as possible at the same time on each day.[3]

Six weeks after publication of this article—on April 14, 1876—Frederick Ensor, Surgeon to the Provincial Hospital in Port Elizabeth, South Africa, began a letter to Maclagan: "I have seen with much interest your papers in *The Lancet* on the 'Treatment of Rheumatism by Salicin,' and thought that the following story might be welcome." Dr. Ensor described his experience with a Dutch Boer patient:

. . . bound hand and foot . . . in the cruel bonds of as fierce an attack of rheumatic fever as I ever saw . . . I prescribed the usual alkaline mixture, with calomel and Dover's powder at bed-time and rode away.

Some two months after, my former patient entered my surgery, looking well, and I very naturally congratulated myself and her that she had recovered so completely. I was quite taken aback when she bluntly told me that my physic hadn't helped her a bit. On inquiring what had helped her, she said that the old Hottentot shepherd had made her a decoction of the shoots of the willows which grow on the banks of the river, and after taking this for a few days she began to get better.

Your papers in *The Lancet* brought the picture of the stout Dutch woman back to my memory. I afterwards learned that a decoction of willow-tops is a favourite remedy for fever, and for what the Boers and native Hottentots call 'sinken kors' or rheumatic fever.[4]

This letter from Dr. Ensor was published in *The Lancet* for June 17, 1876, and the following comments from Dr. Maclagan were appended:

If what has already been published regarding the efficacy of salicin as a remedy for acute rheumatism should be confirmed by a more extended experience —as I have not the least doubt it will be, —it will form a curious commentary on our civilisation, and on the advance of medical science, that one of the most common and painful diseases of the civilised world should have remained one of the opprobria of medicine for many years after a remedy for it was known to the rude Hottentots of South Africa. Equally within the reach of both has ever been the means of cutting short the disease; but the untutored Hottentot shepherd used the proper means, while the accomplished European physician was trying this, that, and the other remedy, with results so unsatisfactory that he had almost given up the idea of ever being able to do more than watch the natural progress of the malady.[4]

By a strange historical coincidence, in 1876—the very year in which Maclagan first reported the efficacy of salicin in the therapy of acute rheumatic fever—there appeared in Germany several articles describing the successful treatment of acute rheumatism with salicylic acid.[3] Several writers mentioned the fact that salicylic acid produced irritation and erosion of the mucous membranes of the esophagus and stomach; others found no such effects. Stricker, of Berlin, attributed these side-effects to impurities such as carbolic acid and maintained that perfectly pure salicylic acid was free from this objectionable action. Riess dissolved the salicylic acid in rectified spirit and glycerin. Another method was to administer it as salicylate of soda, the acid being given with either phosphate or bicarbonate of soda. This compound was said to be tolerated better than the pure acid and to be equally as effective.

The publication of Maclagan's initial article on the use of salicin[3] resulted almost immediately in the confusion of salicin with salicylic acid, as well as in heated controversies over the relative merits of these two drugs. No less a personality than Dr. William H. Broadbent, the noted cardiologist, appears to have confused the two. He wrote in *The Lancet* for April 8, 1876:

Few diseases have had brought against them a heavier armament of drugs than has acute rheumatism. It has been stormed by alkalies and salines, attacked by acids, assaulted by perchloride of iron and quinine, surprised by propylamine and elayl-

chlorure, drained by venesection and purgatives, flooded alternately with hot and cold water, alarmed with blisters, blasted with hot air, lulled by opium, and appeased by chloral hydrate. In addition to these it has been constantly harassed by the raids of lesser foes, such as lemon-juice, citric acid, belladonna, and iodine of potassium. Now another apparently powerful enemy has appeared.[7]

Dr. Broadbent reported four cases in which excellent results were obtained from the administration of salicylic acid, 7½ grains every six hours; this drug made acute rheumatism an affair of only two or three days. It did not have any injurious after-effects, although the patients did complain that it was hot and irritating to the throat. Dr. Broadbent concluded: "It was impossible not to be astonished with the effects, and notwithstanding the many disillusions experience in medicine brings, not a few of which have been furnished by acute rheumatism, I should not do justice to my convictions were I not to say that apparently we have in salicylic acid, as Dr. Maclagan has said in his communication, a remedy for rheumatic fever comparable to quinine as a remedy for ague."[7] Within two days Maclagan replied to *The Lancet* that he thought Broadbent scarcely did him justice when he implied that Maclagan had "simply followed the practice and confirmed the results of the German physicians," Stricker and Riess.[8] Maclagan would be obliged to have Broadbent peruse more carefully the papers published on March 4 and 11, 1876, in which he would find that Maclagen wrote about salicin, not salicylic acid; that he had been using salicin steadily in rheumatic fever since November, 1874, more than a year before Stricker and Riess reported favorably on salicylic acid, and, furthermore, that Maclagan had been using salicin for some time before the use of salicylic acid was introduced into England.[8]

Interestingly enough, on the day before Maclagan wrote the letter just mentioned, Broadbent penned one of apology, dated April 9, 1876, to the editor of *The Lancet*. In it he explained that his case reports were written before he had read Maclagan's article and that his comments concerning Dr. Maclagan's communication had been hurriedly inserted into the paper at the last moment. Broadbent graciously stated that Maclagan's salicin treatment was "clearly original, and I shall be glad if he can establish priority."[9] He was happy to add a note from Dr. H. Senator of Berlin stating the latter's preference for salicin over salicylic acid.

The editor of the *British Medical Journal* of May 6, 1876, concluded that both salicin and salicylic acid, given in pure form or combined with soda, held promise as valuable agents in the treatment of rheumatic fever.[10] This editorial prompted Maclagan, on May 20, 1876, to express his opinion on the relative merits of salicin and salicylic acid. "As I am probably the only person who has had experience of both salicin and salicylic acid in the treatment of acute rheumatism . . . I may be allowed space for a few remarks on the respective merits of these two remedies."[11] The editorial had conveyed the impression that salicylic acid was preferable to salicin and that the beneficial action of salicin was due to its being converted into salicylic acid in the blood. Such a conclusion, according to Maclagan, was definitely erroneous. He felt it more probable that both were split up into some third substance, which was the true remedial agent. He had prescribed salicin in at least 100 different cases and did not recall a single instance in which any disagreeable effect was noticed. He himself had experimented by taking 60 grains morning, noon, and night without feeling the least discomfort. The smallest pinch of salicylic acid, however, gave him a feeling of heat and irritation in his throat, and a dose of 10 grains upset his stomach and burned the base of his tongue. "Salicin is a pleasant bitter, and is best given mixed with a little water, flavoured with syrup of orange if desired. In adequate dose—say 15 grains every two hours—it cuts short an attack of rheumatic fever, without producing disagreeable effects. It should be continued in smaller doses during the first fortnight

of convalescence."[11] Maclagan's conclusion was that, while salicin and salicylic acid seemed to be equally efficacious as remedial agents in acute rheumatism, the former had the advantage of producing no unpleasant effects.

There followed over the next three years numerous exchanges of letters between Senator[12] and Maclagan on the relative merits of salicin and salicylic acid, and Maclagan finally was compelled to note:

> The whole question is too young for anything like dogmatic assertion. I do not say that my views are correct. I give my facts, and I give my interpretations of these facts. Probably many years will elapse, and many others, more competent, share the work, before either the chemistry or the therapeutic effects of the salicyl compounds are properly understood. That many of these compounds, besides salicin and salicylic acid, will be found useful, I entertain no doubt.[13]

In 1881 Maclagan summarized his studies on rheumatic fever in a monograph entitled "Rheumatism: Its Nature, Its Pathology, and Its Successful Treatment."[14] In it he presented arguments refuting the "lactic acid theory" and set forth his views of the germ theory, namely, that many diseases are due to the presence and propagation in the system of minute organisms having no part or share in its normal economy. The "malarial" nature of rheumatic fever was discussed extensively. Maclagan felt that the virus of rheumatic fever was probably a living organism. His description of the pathologic changes may be summarized as follows:

Rheumatic fever is manifested mainly in the inflammation of the fibrous structures of the locomotor and vasculomotor apparatus. The fibrous structures of the serous membranes suffer primarily. The reason for the selection of the cardiac valves is that the inflammatory swellings starting from the fibrous attachments and involving the fibrous frameworks so swell the valve cusps that in closure they unduly rub against one another and induce the changes in the serous surfaces of contact with production of vegetations. The valves of the left side suffer more than those of the right because of the greater strain imposed upon them.

Maclagan stated that myocarditis, while never secondary to endocarditis, might be secondary to pericarditis. He felt that muscle structures could be attacked directly by the rheumatic poison. He reiterated his convictions about the use of salicin in the treatment of acute rheumatism and emphasized the importance of giving large doses in order to keep the system saturated. Whereas hospitals at that time kept their rheumatic patients bedridden for at least four weeks, Maclagan advised keeping the patients in bed for only a week. He felt that salicin was directly destructive of the rheumatic virus and, when used early, could sometimes circumvent cardiac inflammations.

In December, 1882, Maclagan conducted a discussion of salicyl treatment before a meeting of the Medical Society of London. By that time it was clear that his treatment for acute rheumatism was universally accepted in the British empire. A survey of 59 hospitals in Great Britain, each with 100 beds or more, showed that 39 of the 45 hospitals which responded used salicyl treatment, 2 had had no experience with acute rheumatism, 2 declined to give information, and 2 had not tried the treatment. Maclagan pointed out that the salicyl compounds were both antirheumatic and antipyretic. The antirheumatic action, he felt, was the important one in effecting cures. If only the antipyretic action were required, "the external application of cold or the internal administration of quinine" would be sufficient to arrest acute rheumatism.[15] Maclagan emphasized again the importance of administering large doses over a sufficient period of time. He warned that relapses would occur if the treatment were not kept up for some time after the symptoms had subsided. He clearly differentiated between acute, relapsing, and chronic rheumatism.

Maclagan's next publication on rheumatism was a letter published February 24, 1883,[16] in reply to a paper by a Dr. Sansom.

Maclagan took issue with Sansom's opinion that the cardiac inflammation of acute rheumatism was not reversible. He stated that everything which recovers in the joint also recovers in the heart, except the endocardium. According to Maclagan, the endocardium is a nonvascular membrane in which inflammation does not spread. When it is affected with acute rheumatism, there is no general inflammation of its surface and the trouble is limited to a small part of the surface of the affected valve. Maclagan believed that the valvular lesions of rheumatic carditis were caused not by the direct effect of the rheumatic poison on the endocardial lining but by the mechanical action of the valvular ligaments rubbing against one another. This was a condition over which no drug could possibly exercise control, since it was only indirectly of rheumatic origin. Maclagan, however, felt that the early administration of salicyl compounds could prevent the inflammation and subsequent thickening of the fibrous texture of the valves, so that the heart as well as the joints could be saved from injury. He continued to maintain his preference for salicin, because it could be given in larger and more frequent doses than salicylic acid or salicylate of soda.

Maclagan's final paper on the treatment of acute rheumatism was published in *The Lancet* in 1900,[17] just three years before his death. He still felt compelled to maintain his priority in the use of salicin for the treatment of acute rheumatic fever. He took issue with a recent statement that "Dr. Maclagan was the first in England to substitute salicin for salicylates."

Thus, for a period of 26 years—from 1874 until 1900—Thomas J. Maclagan maintained an active interest in salicin. There appears to be no doubt that his observations on the treatment of acute rheumatism by salicin were made independently of any other investigator and that they preceded by at least one year the German observations on the use of salicylates in rheumatic fever. Yet Maclagan's name has been forgotten, and his contributions are not even mentioned by subsequent workers. In Hanzlik's review of the "Actions and Uses of Salicylates and Cincophen in Medicine," [18] Maclagan's original article is listed only under "References not used in the text."

Maclagan was a prolific writer. He published three monographs: "The Germ Theory of Disease," in 1876; "Rheumatism: Its Nature, Its Pathology, and Its Successful Treatment" in 1886, and, in 1885, "Fever, A Clinical Study." The wide range of his medical interests is shown by the subject matter of a few of his other papers: the antimalarial action of the cinchona compounds, pyrexia and hyperpyrexia, typhoid fever, the pathogenesis of cholera, and the therapy of influenza with salicin.

Very little is known of Thomas J. Maclagan as a man. He was the son of another Thomas Maclagan, who, after a very successful career as a medical man in Jamaica retired to Scone, in Perthshire. The younger Maclagan received his early education at a school in Perth. He studied the humanities at Glasgow University and afterward went to Edinburgh to study medicine. He received his medical degree in 1860 and spent some time in further studies in Paris, Munich, and Vienna. In Paris he became interested in the work of Charles Bouchard and, in 1872, translated from the French Bouchard's monograph, "A Study of Some Points in the Pathology of Cerebral Hemorrhage," writing the preface and footnotes to the English edition.

On returning home from France, Maclagan first held a resident appointment at a hospital in Jersey and afterward became Medical Superintendent at the Dundee Infirmary, beginning his work there during a severe epidemic of typhus fever. After three years at this post, he began his successful practice of medicine at Dundee and at the same time was one of the Examiners in Medicine at the University of Aberdeen. It was while he was practicing in Dundee that he wrote his original article on the

therapy of rheumatic fever with salicin. About 1879, he moved to London and established himself at Cadogan Place. He soon acquired an imposing semi-consultant practice. The Duchess of Albany and Thomas Carlyle were among his patients.

On March 20, 1903, at the age of 65, he died of inoperable carcinoma of the stomach at his home in London. He was buried on March 24 at Working, the first part of the burial service being held at St. Paul's, Knightsbridge.[19] It is said that the most famous physicians of the time attended his funeral. He left a widow, three sons, and a daughter.

On the first anniversary of Maclagan's death, James Knowles, editor of the *Nineteenth Century*, asked Dr. William Broadbent to write a further tribute to his memory. Dr. Broadbent wrote in the issue for May, 1904:

> Dr. Maclagan furnished a striking instance of the influence which opportunity and circumstance exercise upon a man's career. He stood at the head of his own department of the medical profession—that of the family physician. Had he been on the staff of one of the great hospitals and medical schools, the same qualities of intellect and character which placed him in that position would certainly have carried him to a prominent place among the leaders of the profession as a whole.
>
> The physician in general practice finds the claims upon his time so exacting that he has little opportunity for original work. He has not, moreover, the wide and varied field of observation afforded by the wards of the hospital or the services of house physician and clinical clerks in the continuous observation and minute record of symptoms. . . .
>
> It is in this kind of work that Dr. Maclagan would have shone, in virtue of the accuracy and keenness of observation, the penetrating insight into the problems of disease, the critical acumen, constructive capacity, and power of lucid exposition which he possessed.
>
> Dr. Maclagan's chief title to a niche in the temple of medical science is in his recognition of rheumatism as belonging to the miasmatic rather than to the eruptive class of fevers, and his perception of its close analogies with malaria which led to his introduction of salicin as the remedy; but his study of fever displays the remarkable intellectual qualities by which he was distinguished.
>
> I have said that Dr. Maclagan stood at the head of his own department of the medical profession. I am not sure that he had the largest practice, extensive as his was. He lacked one element which goes far to constitute the fashionable family doctor—a touch of charlatanism; of this there was in him no faintest trace.
>
> Dr. Maclagan was not possessed of . . . flexibility of adaptation, but was honesty and straightforwardness personified. Happily, these qualities are not rare in the medical profession, but they were exemplified in Maclagan in so high a degree as to constitute an additional distinction and title to respect.[1]

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Contributions of Basic Science to Modern Medicine

The Significance of Nonesterified Fatty Acids in Plasma

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Recent studies have clarified some aspects of fatty acid transport. The results promise to be of clinical importance, since fat, as a major energy source and as a component of body structure, plays a central role in chronic diseases of metabolism. For example, obesity can be conceived as an abnormal balance between the total amount of fatty acid stored in adipose tissue and its availability as substrate for working cells. Arteriosclerosis is characterized by abnormal deposits of fatty acid esters. Diabetes, although usually defined by high blood sugar, is in fact a general disturbance of metabolism, and its most dangerous complications can be traced to faulty handling of fatty acids.

During the past few years a number of laboratories, including ours, have been studying a fatty acid fraction which is remarkable for both its speed of turnover and its close relation to the state of carbohydrate metabolism. This fraction, the nonesterified fatty acids (NEFA), comprises only about 5% of the plasma fatty acids. Until recently it was considered negligible, but of course the functional importance of any constituent must be judged by its metabolic activity rather than its size. The turnover of NEFA measured by the clearance of albumin-bound C^{14}-labeled palmitic acid, is so rapid (half-time about two minutes) [1] that the flux of calories carried in this fraction appears to be more than twice the caloric value of glucose transport.[2] The concentration of NEFA changes sharply in response to insulin,[3] glucose,[3,4] epinephrine,[3,4] and tolbutamide,[5] apparently because these agents affect the rate at which fatty acids are released from depots.

The central facts so far established are these:

1. The NEFA fraction is composed of long-chain fatty acids, about 85% of which have either 16 (palmitic) or 18 (stearic, oleic, and linoleic) carbon atoms.[6] The pattern of fatty acids in NEFA is approximately the same as that of the fatty acids in triglycerides circulating as neutral fat or deposited in adipose tissue.[7]

2. When the concentration of NEFA falls after an injection of insulin, the major components of the fatty acid mixture (palmitic, oleic, and stearic) decrease proportionately.[6] This finding provided some justification for use of labeled palmitic acid as representative of the whole NEFA fraction —at least in studies of the insulin response and closely related processes. However, it must be remembered that there are marked differences in the chemical properties of various fatty acids, especially between the saturated and unsaturated ones. It would be very surprising indeed if further work failed to reveal significant differences in their metabolism. The reservation must be held in mind, since almost all tracer studies reported to date have been limited to the use of palmitic, a saturated acid.

3. When injected in tracer dose, palmitic acid distributes into an initial pool approximately equal to plasma volume and disappears from it with a half-time of about two minutes [1,8]—a rate corresponding to com-

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plete replacement of all circulating NEFA every three minutes. Collection of respiratory CO_2 after injection shows that some of the labeled material is oxidized almost immediately, the quantity being strongly dependent on the state of carbohydrate metabolism.[9] As is the case after injection of labeled triglycerides, starved animals oxidize a large portion of administered fat within a few hours, while animals loaded with dextrose or pretreated with insulin oxidize only a small part and retain the rest in their tissues.[10] Analyses of tissues at various times after injection of C^{14}-labeled palmitic acid, dissolved in homologous serum, showed extensive distribution in many organs, especially liver, with esterification of labeled palmitate into the three main classes of lipids—neutral fat, phospholipids, and cholesterol esters.[11]

4. After injection of the palmitate in fasted rats, little or no activity was detectable in fat depots (perinephric and subcutaneous). The finding is compatible with the theory that the increased amount of circulating NEFA in fasted animals comes from adipose tissue and is being delivered to other organs. In vitro, adipose tissue takes up little or no labeled stearic acid from serum if the animal donating the tissue has been fasted in advance of the experiment, while adipose tissue from fed animals shows a brisk uptake.[12] Measurements of arteriovenous difference in human subjects have demonstrated a removal of NEFA by heart and liver and a contribution of NEFA by some other tissue, presumably adipose, drained by the saphenous vein.[13] These studies, showing different sites of uptake and release, provide the chief evidence that the NEFA fraction is part of a directed transport system and not merely a pool with rapid random mixing.

5. Control of NEFA concentration in plasma appears to be exerted at the point of release from adipose tissue. The clearance of labeled palmitate is unaffected when the concentration of total NEFA is halved by the injection of insulin, while the specific activity of the fraction rises because of a reduced input of unlabeled material from the depots.[8] Insulin abolishes the increment usually found in saphenous vein blood,[13] and in vitro it diminishes the release of fatty acids from adipose tissue.[14]

6. While circulating in plasma the NEFA fraction is carried by albumin.[3,14] Undoubtedly the linkage to a large molecule is of importance in governing the distribution of these fatty acids and in detoxifying what would otherwise be a poisonous accumulation in the blood.[15] The quantity present is roughly equimolar with albumin, well within the binding capacity of that protein.[16]

7. In normal subjects an injection of either insulin or dextrose causes a sharp fall of NEFA but, in the two cases, opposite effects on blood glucose concentration. The common factor responsible for the fall of NEFA appears to be an increased utilization of glucose for synthesis of triglyceride in adipose tissue, which favors retention of the fatty acids in ester form and thus reduces their outflow into the blood plasma. Study of all available data shows a consistent time relation between changes in NEFA and glucose: after insulin these two variables fall and later rise along closely parallel curves; after glucose (or glucagon) the variables show an equally close correlation—but with the difference that the variations are inverse and the curves are mirror images of each other.

8. Study of other agents has yielded results of some pharmacological interest. Both epinephrine[3,4] and dextro-amphetamine[17] cause a sharp rise in NEFA, possibly a counterpart of their calorigenic and appetite-depressing actions. Tolbutamide, used for control of blood sugar in diabetes, causes a fall in concentration of NEFA that is correlated with the fall in sugar.[5] As is well known, normals and subjects with relatively mild diabetes show lowered blood sugar when treated with the drug, while the brittle juvenile type of diabetic is refractory. The change (or lack of it) in concentration of NEFA parallels the response of blood

sugar, thus emphasizing the intimate relation between utilization of glucose and control of fatty acid metabolism.

9. This relation has been further brought out in recent studies of diabetic ketosis. The impairment of fatty acid synthesis in the diabetic liver—which has long been known[18]—appears now to be explained by a block in the reduction of a 4-carbon unsaturated intermediate, crotonyl-Co A (Coenzyme A), to the corresponding saturated compound, butyryl-Co A.[19] This reductive step seems to require reduced triphosphopyridine nucleotide,[20] which is generated in reactions coupled with oxidation of carbohydrate, especially oxidations via the hexose monophosphate pathway.[21] Thus, in a somewhat indirect way, a lack of insulin stops fatty acid synthesis at the 4-carbon stage and leads to an abnormal accumulation of the partially oxidized 4-carbon acids, β-hydroxybutyric and acetoacetic.

However, this is only one aspect of the problem. Ketone acids, produced by the liver, are rapidly taken up in peripheral tissues and utilized by them, even in the extremity of diabetic acidosis. Calculation of the rate at which ketone acids must be produced in order to exceed the rate of peripheral oxidation suggests that a simple block of hepatic lipogenesis would not yield enough of these acids to cause a marked accumulation in the blood.[22] Therefore, in addition to an impaired capacity for synthesis, it appears that the liver of the ketotic patient must be overloaded with fatty acid substrate. Strikingly high values of NEFA are encountered in ketosis[23]; with adequate amounts of insulin the level falls sharply, paralleling the response of glucose and anticipating by several hours the much slower elimination of ketone bodies.[24] The results suggest that the crucial fault in diabetic acidosis is deficient utilization of carbohydrate in adipose tissue leading to an uncontrolled outflow of fatty acids from storage. In less degree the same fault is manifest in the ketosis of fasting, which presumably arises from lack of carbohydrate, since small amounts of glucose—almost unimportant as reckoned in caloric value—relieve the condition[25] and cause a fall of NEFA.[3,4]

Studies now under way in several laboratories should soon clarify the relation of NEFA to the various kinds of esterified fatty acids. The functional relation of NEFA to plasma triglyceride obviously is close; labeled palmitate in the triglycerides of chylomicra rapidly enters the NEFA fraction,[1] and, like NEFA, the triglycerides in alimentary lipemia are lowered by glucose.[26,27] Almost surely there are equally important relations with phospholipids and cholesterol esters, but little is known, apart from the fact that labeled palmitate after injection into the bloodstream rapidly becomes incorporated into them. Perhaps in learning more about NEFA we will come to know more about the function of these mysterious compounds and about the integration of lipid metabolism as a whole.

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Books

Edited by William B. Bean, M.D.*

Antikoagulantien. By Prof. Dr. Eberhard Perlick. Pp. 290. Price, 36 marks. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C. 1, 1957.

Guided no doubt by the famous statement of Cruveilhiers "La phlébite domine en quelque sorte la pathologie tout entière," which he quotes in the summary, Professor Perlick in his monograph presents the broad aspects of thromboembolism as the background for his main topic: anticoagulants. A fairly detailed discussion of the coagulation reaction, including many of the newest concepts and proposed factors, serves as the introduction. This is followed by a comprehensive account of the common anticoagulants. It includes the biochemistry, physiological action, toxicity, therapeutic indication, and control.

A section devoted to the nervous and hormonal factors in their relation to blood coagulation is stimulating and informative, as is to be expected, since Professor Perlick himself has been an important contributor to this field. Unfortunately, a little too much importance is attached to the significance of the clotting time. The meticulous review of the old literature is of dubious value. Thus, the early studies of the action of epinephrine and other hormones on the clotting time are full of contradictions. Even recent works do not entirely escape this failing. The author cites the report that epinephrine normalizes the strongly depressed prothrombin activity from Dicumarol but fails to record that this claim could not be confirmed.

The second half of the monograph is devoted to the pathology of thrombosis and its clinical aspects. A few well-chosen illustrations add greatly to the clarity of the presentation. Both venous and arterial thrombosis are discussed thoroughly in regard to the clinical findings and treatment. Separate sections are devoted to pulmonary embolism, to coronary thrombosis, and to cerebral thrombosis.

The author has crowded into 236 pages of text a tremendous amount of documental information. The book has the advantage of having a unified point of view throughout but also the disadvantage, as even the author himself states in the preface, of having in parts a one-sided presentation. This is no condemnation, since in as complex a field as thrombosis, only a Solomon could be wholly impartial. It is hoped that the language barrier will not limit the reception of this book to the German-speaking countries.

ARMAND J. QUICK, M.D.

Surgery in World War II: Hand Surgery. Edited by Sterling Bunnell, M.D. Price, $3.75. Pp. 447, with 224 illustrations. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1955.

It needed the stimulus of a world war to show that hand wounds are best treated by segregation and care in specially established centers. This book records the achievements of this specialized branch of surgery and is a worthy record of what was probably one of the most remarkable advances in surgery during World War II.

Hand surgery is an area specialty, not a tissue specialty, and therefore needs a surgeon who has been trained in the three disciplines of orthopedic surgery, plastic surgery, and neurosurgery. Such men are rare and were hard to find when the centers were created. However, the surgeons who staffed these centers, and all of whom were pioneering in this new field of surgery, produced conclusive evidence that reconstruction of hands can be successfully undertaken and that crippled hands are worth salvaging.

The book is in two parts, the first of which records the history and organization of the service and summarizes the conclusions reached by the various centers. The second part of the book consists of individual reports from the nine centers for hand surgery which were established in the United States. The surgeon in charge of each unit has been responsible for the writing of his own section, and it is inevitable that there must be considerable variation in style and repetition of various points. This repetition in no way detracts from the value of the book, and for those working in this field it proves to be a very valuable discussion of the various possible methods of treatment. Because of this, it is no textbook but is, nevertheless, full of fundamental points of surgical care of the hand which unfortunately have yet to appear in standard texts of surgery.

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The guiding genius behind the whole of the development of hand surgery in the United States was the late Dr. Sterling Bunnell, and although this book was published under his editorship before his recent death, it can now be considered a very fitting memorial to his pioneer work and must in years to come become a necessary reference book for hand surgeons.

ADRIAN E. FLATT, M.D., F.R.C.S.

Surgery in World War II: Orthopedic Surgery in the Mediterranean Theater of Operations. John Boyd Coates Jr., editor in chief; Mather Cleveland, editor for orthopedic surgery. Price, $4. Pp. 368, with 96 illustrations. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1957.

It is sad but apparently axiomatic that historians of military medicine should preface all their efforts by recording how the concepts and methods of civilian practice were found to be inapplicable to the campaign they report and that appropriate treatment had to be relearned in the field.

This volume is no exception but does record in a very comprehensive manner the care given by the orthopedic services in the Mediterranean area during World War II. Many of the points it raises would only be of interest to an orthopedic surgeon, but the account of the development of the consultant services and the reasons behind the dogmatic tone of the circular letters would seem to imply more intelligence in the higher echelons than junior medical officers are often prepared to allow.

Dogmas invite controversy, and the disagreements raised by some of the treatment orders are reasonably assessed; in the case of amputations this questioning of the absolute use of the guillotine amputation would seem to have been justified, particularly when it is recorded that ninety-five per cent of the stumps needed revision before an artificial limb could be fitted. The pressure of field commanders and logistics inevitably influence treatment, but the orthopedist will find many useful tabulations of results and related discussions reported and will be aided by the comprehensive index.

ADRIAN E. FLATT, M.D., F.R.C.S.

Atomic Energy in Medicine. By K. E. Halnan, M.D. Price, $6. Pp. 157, with 14 illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1957.

The use of ionizing radiation in the treatment of disease is presented in a loose narrative style. In spite of the title, the material covered is not limited to this subject and includes a cursory explanation of such modalities as the cyclotron, betatron, and linear accelerators. The material is presented in an orderly and very readable manner and is surprisingly complete without becoming technical. While an excellent book for the information of the person desiring to broaden his scope of knowledge in this field, it has little to offer the practicing physician toward improving the conduct of his profession.

The book seems ideally suited for the high school or college student desiring basic information on the subject of atomic medicine.

H. B. ELKINS, M.D.

Halsted of Johns Hopkins: The Man and His Men. By Samuel James Crowe, M.D. Price, $5. Pp. 247. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

The long hand of the influence of Johns Hopkins grows with time. The forces determining this man's extensive and extending influence have been analyzed on many occasions by able historians and loyal disciples of the "great men of the Hopkins." Suffice it to say that the development of our modern medical school in the sense of a graduate school of higher learning in a university setting and later the expansion of full-time medicine into the clinical years enabled clinical science to achieve its ancient eminence as the mother of sciences. At The Johns Hopkins University it came to fruition guided by several physicians, scholars, and teachers, whose influence still prevails widely. Probably the only one of the great clinicians in the heyday of Johns Hopkins to leave a personal school was William S. Halsted, who exerted equal influence in the intensive training of a protracted residency program and his emphasis on surgery as an exquisite craft, a practical art applying principles of basic research from the laboratory. Experience resulting from the years of dissection, of operating on animals, and of exploring principles and applications of the body's structure and function was epitomized in Halsted. Now, when surgery of the vascular system is an everyday affair, the

pioneering contributions of Halsted must be remembered, as well as the advances he brought to the surgery of hernia, cancer of the breast, and the thyroid and parathyroid glands. His papers were scholarly treatises, supported by extensive research, both experimental and clinical, and the assimilated experience of his painstaking and careful operations and those of his associates. He was gentle with tissues, miserly with hemorrhage, almost overscrupulous in his regard for the minutiae of detail on which so much may hinge. If his ritualistic approach to operation used overmuch time, the results were a living tribute to the reasonableness and wisdom of his surgical philosophy. All of these things and many more are included in Crowe's book, written through the eyes of a devoted pupil and long-time colleague looking beyond faults and focusing on achievements which have reached monumental proportions and have become a part of history. This, then, is not a critical biography but a tribute and a loving tribute to a great man who overcame great vicissitudes to reach greater accomplishments. Despite his austere and crotchety personality, Guy de Chauliac's definition of a surgeon suits him well:

> "Let the surgeon be well educated, skillful, ready and courteous. Let him be bold in those things that are safe, fearful in those that are dangerous; avoiding all evil methods and practices.
> Let him be tender with the sick, honorable to men of his profession, wise in his predictions, chaste, sober, pitiful, merciful; not covetous or extortionate, but rather let him take his wages in moderation, according to his work and the wealth of his patient and the issue of the disease and his own worth."

WILLIAM B. BEAN, M.D.

Technique of Fluid Balance: Principles and Management of Water and Electrolyte Therapy. By Geoffrey H. Tovey. Price, $2.50. Pp. 100, with 12 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

Dr. Tovey says in his preface, "during recent years several books on fluid balance have been published." The actual number of monographs is in excess of forty. One of the first was by Marriott, who had delivered a series of Croomian Lectures of the Royal College of Physicians in London on Dec. 3 and 5, 1946. Marriott was asked to contribute to the series of American lectures and hastened to point out that he was a physician and not a physiologist. He added, "This may, I hope, be taken into account in excusing any defects in presentation of physiology and in explaining the clinical standpoint from which I have written."

He acknowledged the help of Prof. J. L. Gamble, Prof. R. A. McCance, Prof. D. A. K. Black, and others in supplying diagrams and references. The book was short (seventy-five pages), concise, and a real addition to many busy physicians' libraries. Most of the books that followed were longer, and some have been more complete. Now a reviewer cannot safely refer to a book as the most recent addition to the field because of the exponential rate of appearance of these volumes. With apologies to Dr. Tovey, a brief bit of speculation will be made as to the cause of such profligacy. Review of prefaces reveals that some authors have had many discussions of these problems with their colleagues, or have given a series of lectures, or have been requested by many students, or, occasionally, have been awarded a prize for a series of lectures, so that they are now compelled to write a book. If the truth were known, many authors have probably written a book as a form of release of their frustration. They have spent a great deal of time formulating these abstract ideas, so as to treat an occasional patient or to lecture to a group of students, but this outlet seems to be inadequate recompense. With time and close association, selected abstractions become so understandable that it seems the experience should be shared. Dr. Black, in his recent addition to the field, quotes from Marcel Proust, "Each of us finds lucidity only in those ideas which are in the same state of confusion as his own." Many simply do not have the will power to resist writing a book when they have reached a point of "understanding" this abstract subject.

Dr. Tovey says, "Despite the fact that most of these give an excellent account of the subject I have felt compelled to prepare this further monograph. Firstly, I believe there is a need for a shorter account. . . . Secondly, I feel there is a growing tendency to make water and electrolyte therapy too dependent upon the results of blood electrolyte estimations." There are estimated to be less than 3.7×10^4 words in Dr. Tovey's book.

The second proposition is less easily dealt with. There are generalizations in the text which are cogent. For example, attention is called to the deleterious effect on kidney function of a disturbed pH, which may prevent the preferential excretion and reabsorption which normally would correct the patients' fluid and electrolyte imbalance. Another example of clinical acumen, "Sometimes, despite severe oligaemia, the circulation is maintained by compensatory vasoconstriction until there is a sudden and profound collapse. The speed of collapse in such cases may erroneously suggest a cardiac or cerebral catastrophe." Reliable nursing records are emphasized. Forms are presented for use in keeping records. Several appendices supply information regarding units of measurement, composition of various solutions recommended, and rapid simple chemical techniques.

There are many other agreeable aspects of the book which, together with its brevity, recommend it for the physicians hand bag.

There are other more or less objectionable features which undoubtedly will encourage the writing of any number of additional small books in the next one to five years (depending on specific lag time).

One good excuse would be that some recent books have been too short and not sufficiently accurate in the discussion of chemical composition and acid-base problems and their treatment. It is doubtful that edema of intestinal anastomoses can be prevented by perpetuating a deficit of extracellular fluid or that intraarterial infusion of blood has any real advantage over intravenous replacement.

There is a bedside test for urinary sodium with use of zinc uranyl acetate which Dr. Tovey is apparently not aware of. Dr. Tovey says, "It is only when fluids are given via the alimentary tract that the body has any control over the quantity and quality that shall be absorbed." This should be modified to "conscious" patient and "offered" instead of given. The gastrointestinal tract is not perspicacious.

In conclusion, this book can be recommended as better than some and shorter than most.

EDWARD E. MASON.

Transactions, American Society for Artificial Internal Organs: Volume III. Chicago, Illinois, April 14-15, 1957. George E. Schreiner and Stanley J. Sarnoff, Publication Committee. Price, not given. Pp. 96. Georgetown University Printing Department, Washington, D. C., 1957.

Review of these transactions reveals that twelve new members of this society bring its roster to a total of ninety-two. Twenty-two papers are printed in brief. The majority of these are concerned with exchange of gases (CO_2 and O_2) and solutes, such as urea, uric acid, and electrolytes, between human or experimental animal blood and a dialysate which is either gas (for the pump oxygenator) or liquid (in the case of an artificial kidney). In principle and at least in one instrument described, there is little difference between an artificial heart-lung and an artificial kidney. The greatest current effort in further perfection of instruments seems to be concerned with the exchange between blood and gas. Much faster and complete exchange is required here, and, in addition, the problem of gas embolism still poses a challenge in the opinion of some. Although wetting agents allow defoaming of blood which has been mixed directly with the gas, some workers feel that a membrane interposed between blood and gas is safer. Others are studying the effects of air embolism and feel that a false sense of security may exist in using bubbling oxygenators in that neurological changes and even electroencephalographic tracings will not always indicate damage resulting from air embolism. There is continued interest in the chemical changes and secondary effects of these changes on the artificially perfused and dialyzed subjects. The incidence of disturbances in blood pressure and blood clotting are reduced by scrupulous cleanliness and the use of nonwettable materials. Metabolic acidosis from accumulation of lactic acid appears to be due in large part to inadequate oxygen supply to tissues and seems not to be a problem where adequate flow of blood is provided by the machine. The use of homologous lungs for gas exchange has been modified and improved so as to postpone pulmonary edema in the donor lung. Again, the close relationship of gas- and solute-exchange problems is demonstrated in the interest shown in using an isolated lung lobe as an artificial kidney by placing the dialysate in the air passages. The use of a dog's lung as a temporary artificial kidney for man would be a logical next step, although perhaps superfluous where mechanical kidneys are available.

Some work is being done on the production of permanent artificial parts. Nylon crimped woven blood vessel substitutes have been in use for over two years, and the results are

encouraging to those reporting clinical and experimental data. Artificial mitral valves are still in the dog house, but a few workers are making a serious systematic study of such prostheses. Implantable hearts, chiefly confined to the armchair, are creeping onto drawing boards. Permanent lungs are considered impractical at present. Permanent kidneys may reside in bedrooms and require attachment at night while sleeping. Problems of attachment either of blood vessels or of a dialyzing bag buried in the peritoneal cavity are being studied. This is the old problem of maintaining a foreign body in live tissues without foreign-body reaction, walling-off, or extrusion. It is a tough problem, since lumina must be maintained and infection prevented. It is difficult to have cohesion and not adhesion. The first patients to benefit from such advances would require only partial substitution of parts. Initial efforts to assist such patients have been partial perfusion of those seemingly moribund with acute cardiac decompensation. In some instances this little bit of help given at an appropriate time has allowed the patient to attain a better cardiac rhythm and compensation. It may allow additional time for instituting and experimenting with the usual regimens.

The treatment of patients in hepatic coma with an artificial kidney will probably add more to our knowledge of the terminal state of such patients but does not promise sustained improvement in liver function.

There are some signs of virility in the transactions of this young society, and the horizons are out of sight. It should be noted that arteriosclerosis begins in youth. Already some members are treading old ground; at least one member feels even now, "In conclusion, we wonder whether artificial kidneys have not evolved to a point where men rather than the machines are limiting factor."

EDWARD E. MASON.

Surgery in World War II: Ophthalmology and Otolaryngology. John Boyd Coates Jr., editor in chief; M. Elliott Randolph, editor for ophthalmology; Norton Canfield, editor for otolaryngology. Price, $5. Pp. 605, with 135 illustrations. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1957.

This book is the most recently published volume of the official history of the Medical Department, U. S. Army, in World War II. The first and major part of this volume deals with ophthalmology. M. Elliott Randolph is the editor.

The first, and most interesting, chapters are concerned with the administrative aspects and general clinical policies in the Zone of Interior and in the various theaters of operations. During World War II ophthalmology emerged for the first time as an independent specialty in the U. S. Army, and it was not until 1944 that the Ophthalmology Branch of the Surgical Consultants Division was activated. Before that time ophthalmology was attached to the Section of Head Surgery. This unfortunate coupling with otolaryngology—still apparent in this volume—frequently resulted in poor care for eye injuries. Often an otolaryngologist who had no knowledge of ocular diseases was put in charge of a combined eye and ear, nose, and throat clinic. The surgical results were in such instances poor and are called "unsatisfactory" as far as intraocular foreign bodies were concerned. Such a situation is for me—who served during the last war with a Central European army—incomprehensible.

The task for these eye clinics was indeed a staggering one. More than half a million pairs of spectacles had to be issued annually in the Zone of Interior alone. The total number of battle injuries and wounds of the eyes exceeded 8000. The total number of admissions to hospitals and quarters for eye diseases approached a quarter of a million. The development of the acrylic artificial eye and a modern extensive program for the rehabilitation of the blind present the high points in the aftercare of severely injured soldiers.

In the second part of the book the clinical management of various eye conditions is described. This did not materially differ from the civilian practice of ophthalmology at that time. Some of these contributions represent original papers and are of considerable interest. The toxic effects of atabrine on the cornea (producing an edema) were observed in the Pacific theater. The nutritional amblyopia in American prisoners of war held by the Japanese is carefully analyzed. The problem of night-blindness in the Mediterranean Theater and the field defects caused by circumscribed head injuries are discussed in two interesting articles. The paper on plastic surgery is especially valuable and profusely illustrated.

FREDERICK C. BLODI, M.D.

Textbook of Physiology and Biochemistry. Third edition. By G. H. Bell, J. N. Davidson, and H. Scarborough. Price, $12. Pp. 1082, with 706 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore, 1956.

This is one of the clearest and best illustrated textbooks of physiology I have had the opportunity and the pleasure to read. The biochemical portion of this book is on the weak side in reference to its use as a biochemical text as is usually used in this country. But it is adequate for most students and should be a valuable supplement to those who cannot understand the present-day complexities of modern biochemistry. It is a text that it would be well to have on a practitioner's desk. It does not attempt to cover the clinical applications of either physiology or biochemistry. It is an honest straightforward presentation of a basic science. Understand this, and the application will come easily.

STEVEN M. HORVATH, M.D.

Signs and Symptoms: Applied Pathologic Physiology and Clinical Interpretation. Third edition. Edited by C. M. MacBryde, M.D. Price, $12. Pp. 973, with illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1957.

The third edition of "Signs and Symptoms," edited by Cyril MacBryde and a company of distinguished collaborators, keeps up the high level of performance achieved in earlier editions. I can think of no other book which provides such a wide variety of essays on important clinical matters approached on the basis of symptoms and signs rather than on the basis of mechanisms, body systems, or the more orthodox approach of the textbook. About a third of the book is taken up with manifestations of pain of different kinds in various parts of the body. Then there are chapters on the important medical phenomena, such as cough, hemoptysis, dyspnea, tachycardia, palpitation, hypertension, cyanosis, fever, lymphadenopathy, pathologic bleeding, constipation and diarrhea, anorexia, nausea, vomiting, jaundice, nervousness and fatigue, edema, obesity, undernutrition, dehydration, vertigo and dizziness, syncope, disturbances of consciousness and of muscle movement, and pigmentation. It should not be implied that this book merely deals with the practical application of the interpretation of signs and symptoms by rule of thumb or in order "to make a diagnosis." Where mechanisms are known, they are described faithfully and in detail. As is expected in any group of individual essays collected in a book, there is some unevenness and some overlapping, but in general the writing is satisfactory, the information is skillfully presented and in a manner which should make this book mandatory reading or at least part of the medical know-how of every physician no matter what his specialty or sphere of major interest. The undergraduate student would profit greatly by studying this during his clinical years and continue to use it as a reference during internship, later training, and practice. A book of this quality is a real tribute to the American medical profession and an indication that, despite its faults, American medicine has achieved a high level of distinction in the practical arts as well as in the scientific part of medicine.

WILLIAM B. BEAN, M.D.

Liver: Structure and Function. By Hans Popper, M.D., Ph.D., and Fenton Schaffner, M.S., M.D. Price, $20. Pp. 777, with illustrations. The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 330 W. 42d St., New York 36, 1957.

Sometimes I have wondered what was the first laboratory animal. Was it for experimental purposes or for clinical testing? Surely experiments must go back far earlier than Galen or recorded history. Perhaps the first laboratory animal was the sacrificed domestic creature whose liver was inspected for portents and omens. In fact, experimenters with a bemused sense of history still talk of sacrificing animals, though I have not found any altar even in lavishly appointed laboratories. In an ancient practice the experiment actually concerned society as the patient. The liver was studied by the priest-pathologist. It is even possible that roughly valid answers were obtained if a disease were endemic in domestic animals or if colonists going to a new area read bad omens in a diseased liver and so escaped some local epizootic plague. At any rate, since most ancient times the liver has been the focal point of interest and mystery, both of which remain as large factors in medicine today.

Saunders, Budd, Frerichs, Bright, Rolleston, and McNee have all written monographs or books on the liver. Of these, Rollston and McNee has been the outstanding treasure house of miscellaneous lore as well as items of historic interest. For many years the only reasonably current book on liver disease in this country was one by Lichtman, but recently there has

been an outpouring of books—those by Spellburg, Schiff, Sherlock—to mention a few. One would suppose that the field had been covered so well that there would hardly be place for another monograph on liver disease. However, this is distinctly not true. The encyclopedic volume of Popper and Schaffner, with its emphasis on the pathologic aspect of liver disease, supplies a most important need which has not been covered so well in any other books currently available. The orientation of the senior author is that of experimenter and an expert on morphologic pathology. His scholarly contributions to the subject are well known. In this book he calls on his great experience as pathologist at the Hektoen Institute, where are gathered for study the pathological material from the vast clinical resources of Chicago's Cook County Hospital. Popper has the same broad background of experience and scientific erudition which was so important in the contributions of Rokitansky, Morgagni, and Laennec.

Throughout this book newer techniques for studying the morphology and structure of the liver have been applied to the interpretation and understanding of clinical problems. There are 3735 references arranged alphabetically, with the authors and journals given but no title. This detracts from the use of the book as a source book from which to explore the subject under consideration further without looking up all the references. Perhaps the experience and orientation of the author limits the clinical aspect which is not so thoroughly developed. The title, "Structure and Function," indicates the emphasis of this book on morphology and pathology. There is nothing on treatment, and the clinical aspects of hepatic function are discussed briefly. Since much of the information we have about liver function and the pathology of liver disease is unsettled, there are opportunities for differences of opinion and arguments with the writers of this book, though I find fewer occasions for disagreement than I would have expected in a comprehensive volume of this kind. Since treatment and the clinical aspects of liver disease are so little touched in this book, it will appeal primarily to those who are interested in liver disease, gastroenterology, and pathology, and for them it is a most excellent and much needed addition to the reference books now available in liver disease. The photographs and diagrams are clear, and the heavy paper needed for the illustrations mean the book must be read at a desk rather than in an armchair, as befits a monumental work which is a fine tribute to the industry, persistence, knowledge, and thoroughness of the distinguished senior author and his colleague. It will remain an indisposable source book and reference.

WILLIAM B. BEAN, M.D.

Psychological Implications of Current Pediatric Practice. Report of Twenty-Fourth Ross Pediatric Research Conference. Edited by William O. Robertson, M.D. Price, not given. Pp. 76. Ross Laboratories, Columbus 16, Ohio, 1957.

The Twenty-Fourth Ross Pediatric Research Conference, a symposium on psychological implications in current pediatric practice, was held under the auspices of the Department of Pediatrics, Albert Einstein College of Medicine, Yeshiva University, New York, March 1-2, 1957.

As indicated on the front cover of the book, "The purpose of the Ross Pediatric Conferences is to assist in the correlation of the latest information derived from research on subjects of general interest in the practice of pediatrics, and to stimulate further research by an exchange of information and ideas."

Dr. Henry L. Barrett, the chairman of the conference, gathered together a group of persons well qualified to carry out the purpose of the conference, and, as a result, the transcript of the conference is a stimulating and up-to-date description of current practices.

The participants were persons who represented the fields of education, general practice, nursing, obstetrics, pediatrics, preventive medicine, psychiatry, psychology, and social work. Many are nationally known, and all served to present a variety of theories and procedures which merit serious consideration and can usefully be integrated into the practice of the general practitioner.

The discussion was opened by Dr. Lewis Fraad, who presented a summary of his interviews with parents during prepartal visits and visits to the new mother in the immediate postpartum period. As a pediatrician, Dr. Fraad described the advantages of the prepartal visit, especially for a primipara, his procedures during the initial interview, the question of breast-feeding versus bottle-feeding, sources of anxiety for the new mother, and other practical considerations. He presented a very wise, flexible, individual approach to a varied group of problems which appear to the pediatrician during the "getting acquainted period"

and showed much understanding and sensitivity to the psychological implications of his practices.

Dr. Barbara Korsch then focused on the physician-family relationship during the baby's first three months of life and discussed such matters as techniques of obtaining a worthwhile history, both medical and family, feeding problems and the question of scheduled feedings, overpermissiveness, colic, use of the pacifier, sleep problems, techniques of counseling, and other procedures. Dr. Korsch described many useful practices in an interesting and lucid manner.

The remainder of the conference was a general discussion of the material presented and included such items as the psychology of pregnancy, factors influencing maternal attitudes, effectiveness of prepartal classes, use of intuition, sleep arrangement, physiology of sleep, and synthesis of the psyche.

The participants in the conference are to be complimented on their having produced a readable work, eclectic in approach, highly instructive and yet cognizant of the problems that exist and the difficulties involved in gathering meaningful data. I would highly recommend this work for anyone interested in the problems of the prepartal and early postpartal period.

BENJAMIN BLACKMAN, M.D.

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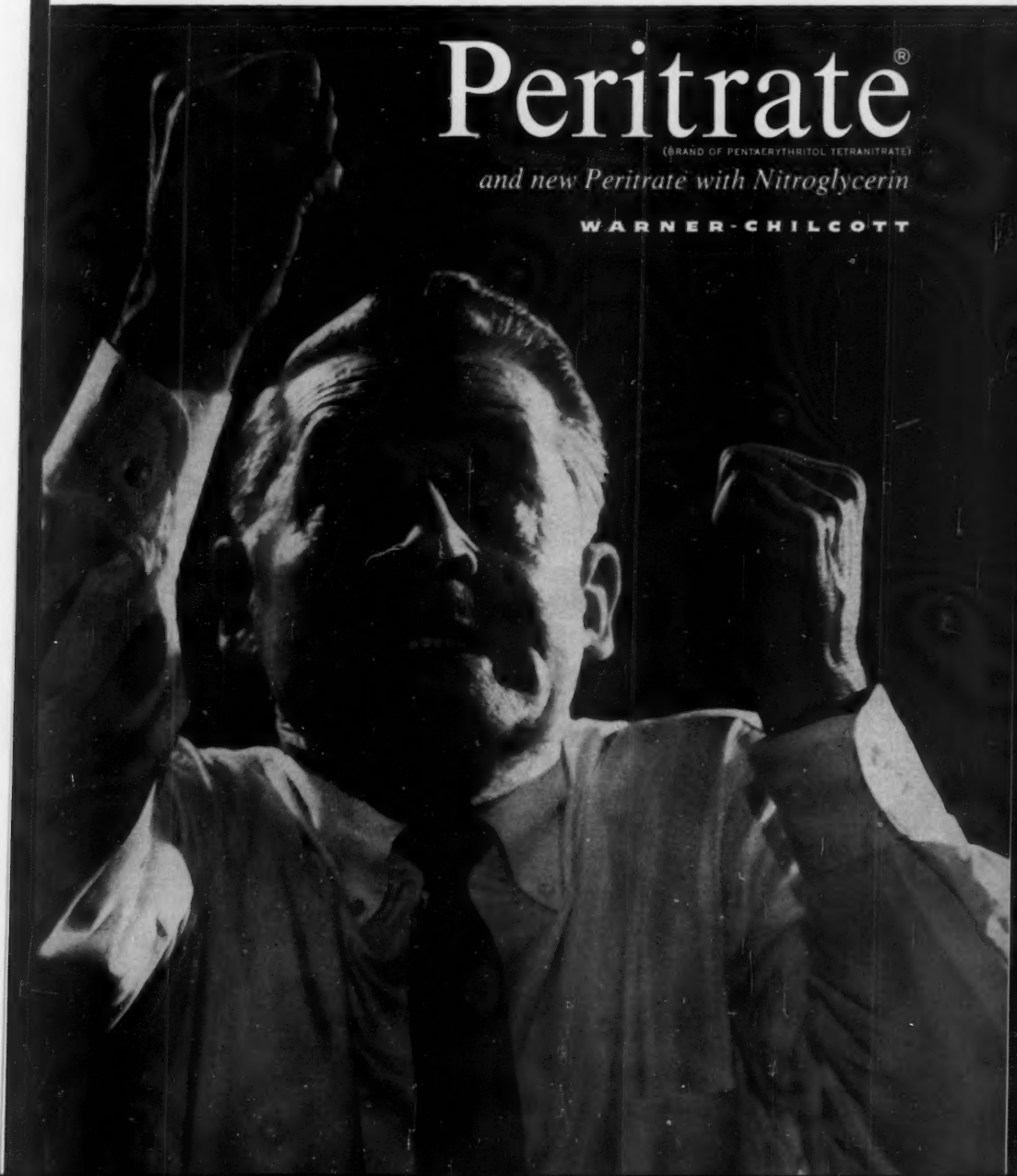

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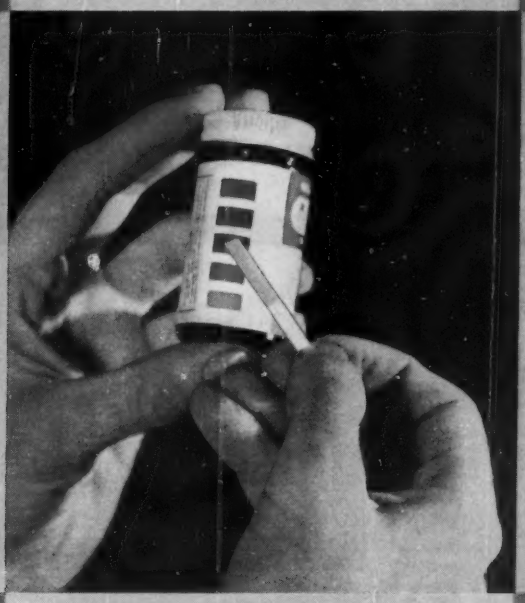

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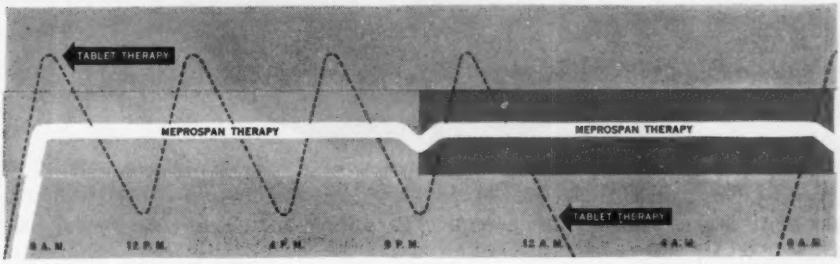

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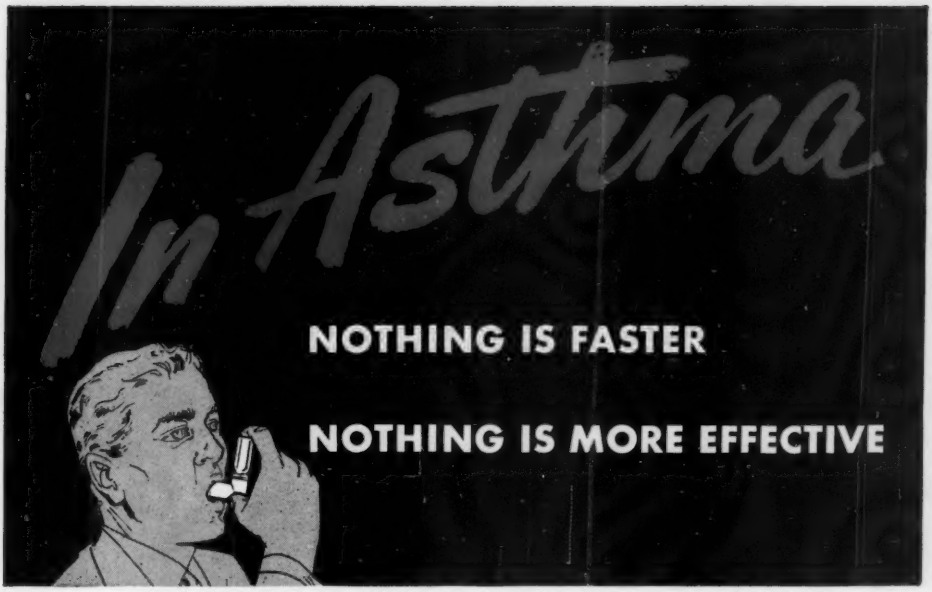

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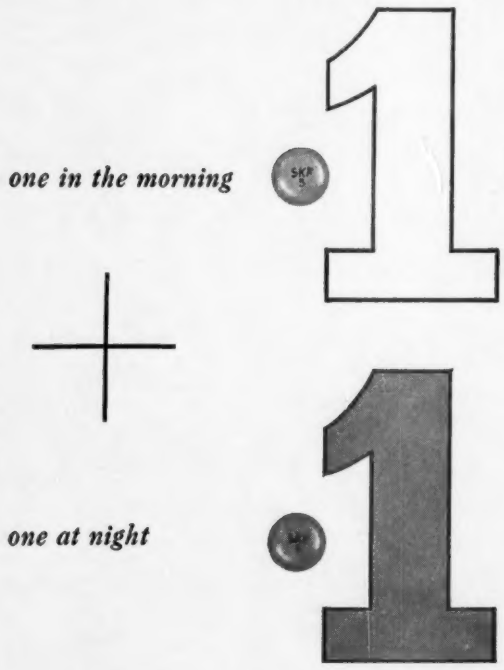

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1. Mullie, A.: The Inhibition of Basal Gastric Secretion and of the Gastric Secretory Response to Histamine by 2,2-Diphenyl-4-diisopropylamino-butyramide Methyliodide ['Darbid'] in Man, Arch. internat. pharmacodyn. *106*:447 (June) 1956.

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